N-[3-(3-SUBSTITUTED-PYRAZOLO[1,5-a]PYRIMIDIN-7-YL)PHENYL]-SULFONAMIDES, AND COMPOSITIONS, AND METHODS RELATED THERETO

Technical field

This invention is directed to agents with affinity for $GABA_A$ receptor, more specifically to pyrazolo[1,5-a] pyrimidines.

Background of the invention

$GABA_A$ receptor (γ-aminobutyric $acid_A$) is a pentameric protein which forms a membrane ion channel. $GABA_A$ receptor is implicated in the regulation of sedation, anxiety, muscle tone, epileptogenic activity and memory functions. These actions are due to defined subunits of $GABA_A$ receptor, particularly the α_1- and α_2-subunits.

Sedation is modulated by the α_1-subunit. Zolpidem is characterized by a high affinity for the α_1-receptors and its sedative and hypnotic action is mediated by these receptors *in vivo*. Similarly, the hypnotic action of zaleplon is also mediated by the α_1-receptors.

The anxiolytic action of diazepam is mediated by the enhancement of GABAergic transmission in a population of neurons expressing the α_2-receptors. This indicates that the α_2-receptors are highly specific targets for the treatment of anxiety.

Muscle relaxation in diazepam is mainly mediated by α_2-receptors, since these receptors exhibit a highly specific expression in spinal cord.

The anticonvulsant effect of diazepam is partly due to α_1-receptors. In diazepam, a memory-impairing compound, anterograde amnesia is mediated by α_1-receptors.

$GABA_A$ receptor and its α_1- and α_2-subunits have been widely reviewed by H. Möhler et al.(J. Pharmacol. Exp. Ther., 300, 2-8, 2002); H. Möhler et al.(Curr. Opin. Pharmacol., 1, 22-25, 2001); U. Rudolph et al.(Nature, 401, 796-800, 1999); and D.J. Nutt et al. (Br. J. Psychiatry, 179, 390-396, 2001).

Diazepam and other classical benzodiazepines are extensively used as anxiolytic agents, hypnotic agents, anticonvulsants and muscle relaxants. Their side effects include anterograde amnesia, decrease in motor activity and potentiation of ethanol effects.

In this context, the compounds of this invention are ligands of α_1- and α_2-$GABA_A$ receptor for their clinical application in sleep disorders, preferably insomnia, anxiety and epilepsy.

Insomnia is a highly prevalent disease. Its chronicity affects 10% of the population and 30% when transitory insomnia is computed as well. Insomnia describes the trouble in getting to sleep or staying asleep and is associated with next-day hangover effects such as weariness, lack of energy, low concentration and

irritability. The social and health impact of this complaint is important and results in evident socioeconomic repercussions.

Pharmacological therapy in the management of insomnia firstly included barbiturates and chloral hydrate, but these drugs elicit numerous known adverse effects, for example, overdose toxicity, metabolic induction, and enhanced dependence and tolerance. In addition, they affect the architecture of sleep by decreasing above all the duration and the number of REM sleep stages. Later, benzodiazepines meant an important therapeutic advance because of their lower toxicity, but they still showed serious problems of dependence, muscle relaxation, amnesia and rebound insomnia following discontinuation of medication.

The latest known therapeutic approach has been the introduction of non-benzodiazepine hypnotics, such as pyrrolo[3,4-b]pyrazines (zopiclone), imidazo[1,2-a] pyridines (zolpidem) and, finally, pyrazolo[1,5-a] pyrimidines (zaleplon). Later, two new pyrazolo[1,5-a] pyrimidines, indiplon and ocinaplon, have entered into development, the latter with rather anxiolytic action. All these compounds show a rapid sleep induction and have less next-day hangover effects, lower potential for abuse and lower risk of rebound insomnia than benzodiazepines. The mechanism of action of these compounds is the alosteric activation of $GABA_A$ receptor through its binding to benzodiazepine binding site (C. F. P. George, The Lancet, 358, 1623-1626, 2001). While benzodiazepines are unspecific ligands at $GABA_A$ receptor binding site, zolpidem and zaleplon show a greater selectivity for α_1-subunit.

Notwithstanding that, these drugs still affect the architecture of sleep and may induce dependence in long-term treatments.

In US patent documents No. 4,626,538 (zaleplon), No. 4,654,347, 6,399,621 (indiplon) and European Patent No. 129,847 (ocinaplon) hypnotic pyrazolo[1,5-a]pyrimidines are disclosed.

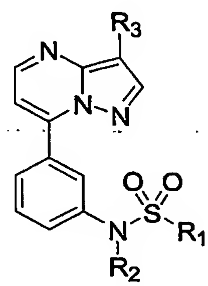
Research for new active compounds in the management of insomnia answers an underlying health need, because even recently introduced hypnotics still affect the architecture of sleep and may induce dependence in long-term treatments.

It is therefore desirable to focus on the development of new hypnotic agents with a lower risk of side effects.

Thus, the present invention is directed to new N-[3-(3-substituted-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-sulfonamides which are active versus $GABA_A$ and, particularly, versus its α_1- and α_2-subunits. Consequently, the compounds of this invention are useful in the treatment and prevention of all those diseases mediated by $GABA_A$ receptor α_1- and α_2-subunits. Non-limitative examples of such diseases are sleep disorders, preferably insomnia, anxiety and epilepsy. Non-limitative examples of the relevant indications of the compounds of this invention are all those diseases or conditions, such as insomnia or anesthesia, in which an induction of sleep, an induction of sedation or an induction of muscle relaxation are needed.

Detailed description of the invention

The present invention relates to novel N-[3-(3-substituted-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-sulfonamides of formula (I)



(I)

and their pharmaceutically acceptable salts;

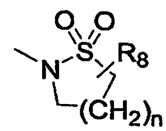
wherein

R_1 is selected from the group consisting of alkyl(C_1-C_6), alkenyl(C_2-C_6), ω,ω,ω-trifluoroalkyl(C_1-C_6), cycloalkyl(C_3-C_6), cycloalkyl(C_3-C_6)alkyl(C_1-C_6), -O-alkyl(C_1-C_6), -NH-alkyl(C_1-C_6), -N(dialkyl(C_1-C_6)), alkyl(C_1-C_6)-O-alkyl(C_1-C_6), alkyl(C_1-C_6)-NH-alkyl(C_1-C_6), alkyl(C_1-C_6)-N(dialkyl(C_1-C_6)), phenyl, monosubstituted phenyl, disubstituted phenyl, phenylalkyl(C_1-C_6), phenylalkenyl(C_2-C_6), furyl, substituted furyl, isoxazolyl, substituted isoxazolyl, pyrazolyl, substituted pyrazolyl, thienyl, substituted thienyl, thiazolyl, substituted thiazolyl, pyridyl and substituted pyridyl;

R_2 is selected from the group consisting of hydrogen, alkyl(C_1-C_6), alkenyl(C_2-C_6), alkynyl(C_2-C_6) and cycloalkyl(C_3-C_6);

or else

R_1 and R_2 form a cycle having the structure:



wherein n is an integer 1, 2 or 3 inclusive;

R_3 is selected from the group consisting of hydrogen, halogen, alkyl(C_1-C_6), cycloalkyl(C_3-C_6), alkenyl(C_2-C_6), alkynyl(C_2-C_6), -O-alkyl(C_1-C_6), halo-alkyl(C_1-C_6), -CN, -SO_2-R_4, -NH-R_4, -NR_4R_5, -COR_6, -CO-NHR_6, -$COOR_6$, -C(NR_7)R_6, phenyl, substituted phenyl, heteroaryl and substituted heteroaryl;

R_4 and R_5 are independently selected from the group consisting of alkyl(C_1-C_6), cycloalkyl(C_3-C_6), aryl and heteroaryl;

R_6 is selected from the group consisting of hydrogen, alkyl(C_1-C_6), alkenyl(C_2-C_6), alkynyl(C_2-C_6), cycloalkyl(C_3-C_6), phenyl, substituted phenyl, furyl, substituted furyl, thienyl, substituted thienyl, thiazolyl, substituted thiazolyl, pyridyl and substituted pyridyl;

R_7 is selected from the group consisting of alkyl(C_1-C_6), cycloalkyl(C_3-C_6), -OH, -O-alkyl(C_1-C_6), alkyl(C_1-C_6)-O-alkyl(C_1-C_6), alkyl(C_1-C_6)-NH-alkyl(C_1-C_6), alkyl(C_1-C_6)-N(dialkyl(C_1-C_6)), phenyl, monosubstituted phenyl, furyl, thienyl, thiazolyl and pyridyl; and

R_8 is selected from the group consisting of hydrogen, alkyl(C_1-C_6), cycloalkyl(C_3-C_6), aryl and substituted or unsubstituted heteroaryl;

with the proviso that:

R_1 may simultaneously not be p-tolyl and R_2 methyl and R_3 benzoyl; and

R_1 may simultaneously not be p-tolyl and R_2 ethyl and R_3 furyl-2-carbonyl.

US Patent No. 4.654.347 (Example 80) discloses N-[3-(3-benzoyl-pyrazolo[1,5-a]pyrimidin-7-yl)phenyl]-N,4-dimethyl -benzenesulfonamide and European Patent No. 129.847 (Example 166) discloses N-ethyl-N-[3-[3-(2-furylcarbonyl) - pyrazolo[1,5-a]pyrimidin-7-yl]phenyl]-4-methyl-benzene-sulfonamide. These compounds are merely recited in the above patents as synthetic intermediates, and they are not considered pharmacologically active substances. This fact, therefore, does not suggest that analog compounds, like those in the instant invention, may be therapeutically interesting, which finding has unexpectedly been discovered by the applicants. These compounds, which are comprised in the general formula (I), have purposely been thus excluded from the scope of this invention.

R_1 is preferably selected from alkyl(C_1-C_6); ω,ω,ω-trifluoroalkyl(C_1-C_6); phenyl; phenyl substituted with 1 or 2 groups which are independently selected from halogen (in particular fluoro and chloro), cyano, NO_2, Oalkyl(C_1-C_6) and alkyl(C_1-C_6); phenylalkenyl(C_2-C_6); cycloalkyl(C_3-C_6); cycloalkyl(C_3-C_6)alkyl(C_1-C_6); phenylalkyl(C_1-C_6); alkenyl(C_2-C_6); isoxazolyl which may be substituted with 1 or 2 alkyl(C_1-C_6); furyl which may be substituted with 1 or 2 alkyl(C_1-C_6); furyl which may be substituted with 1 alkyl(C_1-C_6) and 1 trifluoromethyl; thiazolyl which may substituted with 1 or 2 alkyl(C_1-C_6); pyrazolyl which may be substituted with 1, 2 or 3 alkyl(C_1-C_6); thienyl which may be substituted with 1 or 2 alkyl(C_1-C_6) and pyridyl which may be substituted with 1 or 2 4-morpholinyl groups; or R_1 and R_2 together form the above mentioned cycle wherein n and R_8 are as defined above.

R^2 is preferably selected from H, alkyl(C_1-C_6), cycloalkyl(C_3-C_6) and alkinyl(C_2-C_6), or R_2 forms together with R_1 the above mentioned cycle wherein n and R_8 are as defined above.

R_3 is preferably selected from H, CN and COR_6 wherein R_6 is selected from phenyl which may be substituted with 1 or 2 groups which are independently selected from halogen (in particular fluoro or chloro), alkyl(C_1-C_6) and Oalkyl(C_1-C_6); thienyl; pyridyl and oxadiazolyl which may be substituted with alkyl(C_1-C_6).

A preferred embodiment relates to the compounds of formula I wherein R_3 is cyano, R_1 is selected from alkyl(C_1-C_6), phenyl and phenyl substituted with an Oalkyl(C_1-C_6) group, and R_2 is selected from alkyl(C_1-C_6), cycloalkyl(C_3-C_6) and alkynyl(C_2-C_6).

A further preferred embodiment relates to compounds of formula I, wherein R_3 is thiophene carbonyl, in particular thiophene-2-carbonyl, R_1 is selected from alkyl(C_1-C_6); pheylalkenyl(C_2-C_6); ω,ω,ω-trifluoroalkyl(C_1-C_6); phenyl; phenyl substituted with 1 or 2 groups which are independently selected from halogen (in particular fluoro and chloro), cyano, Oalkyl(C_1-C_6) and nitro; phenylalkyl(C_1-C_6); cycloalkyl(C_3-C_6); alkenyl(C_2-C_6); cycloalkyl(C_3-C_6)alkyl(C_1-C_6); isoxazolyl substituted with 1 or 2 alkyl (C_1-C_6); furyl substituted with 1 or 2 groups independently selected from alkyl(C_1-C_6) and w,w,w-trifluoroalkyl (C_1-C_6); thiazolyl substituted with 1 or 2 alkyl(C_1-C_6); pyridyl which is substituted with a 4-morpholinyl group; thienyl; and pyrazolyl substituted with 1, 2 or 3 alkyl(C_1-C_6), and R_2 is selected from H, alkyl(C_1-C_6), cycloalkyl(C_3-C_6) and alkynyl(C_2-C_6).

A further preferred embodiment relates to compounds of formula I, wherein R_3 is selected from benzoyl, wherein the phenyl group may be substituted with halogen (in particular fluoro or chloro), alkyl(C_1-C_6) and Oalkyl(C_1-C_6); oxadiazolyl which is substituted with alkyl(C_1-C_6) and pyridylcarbonyl; R_1 is alkyl(C_1-C_6) and R_2 is H, alkyl(C_1-C_6) or alkynyl(C_2-C_6).

Preferably, the present invention relates to new N-[3-(3-substituted-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-sulfonamides of formula (I) wherein R_1 is selected from the group consisting of methyl, ethyl, n-propyl, i-propyl, n-butyl, 2-phenylethenyl, 2,2,2-trifluoroethyl, phenyl, 2-clorophenyl, 3-clorophenyl, 4-clorophenyl, 2,4-diclorophenyl, 3,4-dichlorophenyl, 2-cyanophenyl, 3-cyanophenyl, 4-cyanophenyl, 4-methoxyphenyl, 3-nitrophenyl, 4-nitrophenyl, 2-thienyl, 5-methyl-4-isoxazolyl, 5-methyl-2-trifluoromethyl-3-furyl, 4-(4-morpholinyl)-3-pyridyl, 2,4-dimethyl-5-thiazolyl, cyclopropyl, benzyl, vinyl, 3,5-dimethyl-4-isoxazolyl, 1,3,5-trimethyl-4-pyrazolyl and cyclopentylmethyl; R_2 is selected from the group consisting of hydrogen, methyl, ethyl, n-propyl, i-propyl, n-butyl, cyclopropyl and 2-propynyl, or R_1 and R_2 form in conjunction with the -N-SO_2- group an isothiazolidine-1,1-dioxide ring, in such a way that R_1 and R_2 form together a 1,3-propylene group, and R_3 is selected from a cyano group, a benzoyl group, a 4-fluorobenzoyl group, a 4-methylbenzoyl group, a 4-methoxybenzoyl group, a 5-methyl-1,2,4-oxadiazol-3-yl group, a pyridyl-2-carbonyl group, a pyridyl-4-carbonyl group and a thiophene-2-carbonyl group.

"Heteroaryl" means 5- or 6-membered aromatic heterocyclic groups containing 1, 2 or 3 heteroatoms which are independently from each other selected from N, O and S. Examples for heteroaryl groups are pyridyl, pyrimidinyl, triazinyl, pyrrolyl, thienyl, furyl, oxazolyl, thiazolyl, imidazolyl, oxadiazolyl.

"Aryl" means preferably phenyl or naphthyl.

"Halogen" or "halo" means F, Cl, Br or I, preferably F or Cl.

"Cycloalkyl(C_3-C_6)" preferably means cyclopropyl, cyclopentyl or cyclohexyl.

"Substituted" (including mono- and di- substituted) means that the group in question carries 1, 2 or 3 substituents which are independently from each other selected from alkyl(C_1-C_6), Oalkyl(C_1-C_6), halogen, CN and NO_2. In case of heteroaryl groups the substituent may also be attached to a hetero nitrogen atom.

Alkyl groups (also in -Oalkyl, -NHalkyl etc.) include straight chain and branched groups and preferably have 1 to 4 carbon atoms.

The term "pharmaceutically acceptable salt" used herein encompasses any salt formed from organic and inorganic acids, such as hydrobromic, hydrochloric, phosphoric, nitric, sulfuric, acetic, adipic, aspartic, benzenesulfonic, benzoic, citric, ethanesulfonic, formic, fumaric, glutamic, lactic, maleic, malic, malonic,

mandelic, methanesulfonic, 1,5-naphthalendisulfonic, oxalic, pivalic, propionic, p-toluenesulfonic, succinic, tartaric acids and the like.

The preferred compounds of the present invention are shown below:

N-[3-(3-cyano-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-N-methyl-methanesulfonamide;

N-[3-(3-cyano-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-N-ethyl-methanesulfonamide;

N-[3-(3-cyano-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-N-methyl-benzenesulfonamide;

N-[3-(3-cyano-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-N-ethyl-benzenesulfonamide;

N-methyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a] pyrimidin-7-yl]-phenyl}-methanesulfonamide;

N-ethyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a] pyrimidin-7-yl]-phenyl}-methanesulfonamide;

N-methyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a] pyrimidin-7-yl]-phenyl}-benzenesulfonamide;

N-ethyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a] pyrimidin-7-yl]-phenyl}-benzenesulfonamide;

N-prop-2-inyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo [1,5-a]pyrimidin-7-yl]-phenyl}-methanesulfonamide;

N-propyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a] pyrimidin-7-yl]-phenyl}-ethanesulfonamide;

N-ethyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a] pyrimidin-7-yl]-phenyl}-ethanesulfonamide;

N-prop-2-inyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-2-propanesulfonamide;

N-methyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a] pyrimidin-7-yl]-phenyl}-ethanesulfonamide;

N-butyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-ethanesulfonamide;
7-(3-(2-isothiazolidinyl-1,1-dioxide)-phenyl)-3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]pyrimidine;
N-methyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-2-propanesulfonamide;
N-ethyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-2-propanesulfonamide;
N-propyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-2-propanesulfonamide;
N-butyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-2-propanesulfonamide;
N-[3-(3-cyano-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-N-prop-2-inyl-methanesulfonamide;
N-[3-(3-cyano-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-N-propyl-ethanesulfonamide;
N-[3-(3-cyano-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-N-ethyl-ethanesulfonamide;
N-[3-(3-cyano-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-N-prop-2-inyl-propane-2-sulfonamide;
N-[3-(3-cyano-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-N-methyl-ethanesulfonamide;
N-[3-(3-cyano-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-N-butyl-ethanesulfonamide;
7-(3-(2-isothiazolidinyl-1,1-dioxide)-phenyl)-3-cyano-pyrazolo[1,5-a]pyrimidine;
N-[3-(3-cyano-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-N-methyl-2-propanesulfonamide;
N-[3-(3-cyano-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-N-ethyl-2-propanesulfonamide;
N-[3-(3-cyano-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-N-butyl-2-propanesulfonamide;

N-[3-(3-cyano-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-N-propyl-2-propanesulfonamide;

N-[3-(3-cyano-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-N-prop-2-inyl-ethanesulfonamide;

N-methyl-N-{3-[3-(pyridin-2-carbonyl)-pyrazolo[1,5-a] pyrimidin-7-yl]-phenyl}-methanesulfonamide;

N-ethyl-N-{3-[3-(pyridin-2-carbonyl)-pyrazolo[1,5-a] pyrimidin-7-yl]-phenyl}-methanesulfonamide;

N-prop-2-inyl-N-{3-[3-(pyridin-2-carbonyl)-pyrazolo[1,5-a] pyrimidin-7-yl]-phenyl}-methanesulfonamide;

N-methyl-N-{3-[3-(pyridin-2-carbonyl)-pyrazolo[1,5-a] pyrimidin-7-yl]-phenyl}-ethanesulfonamide;

N-ethyl-N-{3-[3-(pyridin-2-carbonyl)-pyrazolo[1,5-a] pyrimidin-7-yl]-phenyl}-ethanesulfonamide;

N-prop-2-inyl-N-{3-[3-(pyridin-2-carbonyl)-pyrazolo[1,5-a] pyrimidin-7-yl]-phenyl}-ethanesulfonamide;

N-methyl-N-{3-[3-(pyridin-4-carbonyl)-pyrazolo[1,5-a] pyrimidin-7-yl]-phenyl}-methanesulfonamide;

N-ethyl-N-{3-[3-(pyridin-4-carbonyl)-pyrazolo[1,5-a] pyrimidin-7-yl]-phenyl}-methanesulfonamide;

N-methyl-N-{3-[3-(pyridin-4-carbonyl)-pyrazolo[1,5-a] pyrimidin-7-yl]-phenyl}-ethanesulfonamide;

N-ethyl-N-{3-[3-(peridin-4-carbonyl)-pyrazolo[1,5-a] pyrimidin-7-yl]-phenyl}-ethanesulfonamide;

N-prop-2-inyl-N-{3-[3-(pyridin-4-carbonyl)-pyrazolo [1,5-a]pyrimidin-7-yl]-phenyl}-ethanesulfonamide;

N-prop-2-inyl-N-{3-[3-(pyridin-4-carbonyl)-pyrazolo[1,5-a] pyrimidin-7-yl]-phenyl}-methanesulfonamide;

N-methyl-N-{3-[3-(fluorobenzene-4-carbonyl)-pyrazolo[1,5-a] pyrimidin-7-yl]-phenyl}-methanesulfonamide;

N-ethyl-N-{3-[3-(fluorobenzene-4-carbonyl)-pyrazolo[1,5-a] pyrimidin-7-yl]-phenyl}-methanesulfonamide;

N-methyl-N-{3-[3-(fluorobenzene-4-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-ethanesulfonamide;

N-ethyl-N-{3-[3-(fluorobenzene-4-carbonyl)-pyrazolo[1,5-a] pyrimidin-7-y]-phenyl}-ethanesulfonamide;

N-prop-2-inyl-N-{3-[3-(fluorobenzene-4-carbonyl)-pyrazolo [1,5-a]pyrimidin-7-yl]-phenyl}-ethanesulfonamide;

N-prop-2-inyl-N-{3-[3-(fluorobenzene-4-carbonyl)-pyrazolo [1,5-a]pyrimidin-7-yl]-phenyl}-methanesulfonamide;

N-methyl-N-{3-[3-(4-methoxybenzoyl)-pyrazolo[1,5-a] pyrimidin-7-yl]-phenyl}-methanesulfonamide;

N-ethyl-N-{3-[3-(4-methoxybenzoyl)-pyrazolo[1,5-a] pyrimidin-7-yl]-phenyl}-methanesulfonamide;

N-methyl-N-{3-[3-(4-methoxybenzoyl)-pyrazolo[1,5-a] pyrimidin-7-yl]-phenyl}-ethanesulfonamide;

N-ethyl-N-{3-[3-(4-methoxybenzoyl)-pyrazolo[1,5-a] pyrimidin-7-yl]-phenyl}-ethanesulfonamide;

N-prop-2-inyl-N-{3-[3-(4-methoxybenzoyl)-pyrazolo[1,5-a] pyrimidin-7-yl]-phenyl}-ethanesulfonamide;

N-prop-2-inyl-N-{3-[3-(4-methoxybenzoyl)-pyrazolo[1,5-a] pyrimidin-7-yl]-phenyl}-methanesulfonamide;

N-methyl-N-{3-[3-(4-methylbenzoyl)-pyrazolo[1,5-a] pyrimidin-7-yl]-phenyl}-methanesulfonamide;

N-ethyl-N-{3-[3-(4-methylbenzoyl)-pyrazolo[1,5-a] pyrimidin-7-yl]-phenyl}-methanesulfonamide;

N-methyl-N-{3-[3-(4-methylbenzoyl)-pyrazolo[1,5-a] pyrimidin-7-yl]-phenyl}-ethanesulfonamide;

N-ethyl-N-{3-[3-(4-methylbenzoyl)-pyrazolo[1,5-a] pyrimidin-7-yl]-phenyl}-ethanesulfonamide;

N-prop-2-inyl-N-{3-[3-(4-methylbenzoyl)-pyrazolo[1,5-a] pyrimidin-7-yl]-phenyl}-ethanesulfonamide;

N-prop-2-inyl-N-{3-[3-(4-methylbenzoyl)-pyrazolo[1,5-a] pyrimidin-7-yl]-phenyl}-methanesulfonamide;

N-methyl-N-{3-[3-(benzoyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-methanesulfonamide;
N-ethyl-N-{3-[3-(benzoyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-methanesulfonamide;
N-methyl-N-{3-[3-(benzoyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-ethanesulfonamide;
N-ethyl-N-{3-[3-(benzoyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-ethanesulfonamide;
N-prop-2-inyl-N-{3-[3-(benzoyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-ethanesulfonamide;
N-prop-2-inyl-N-{3-[3-(benzoyl)-pyrazolo[1,5-a] pyrimidin-7-yl]-phenyl}-methanesulfonamide;
N-methyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a] pyrimidin-7-yl]-phenyl}-2-phenylethenesulfonamide;
N-methyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a] pyrimidin-7-yl]-phenyl}-2,2,2-trifluoroethane-sulfonamide;
N-methyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a] pyrimidin-7-yl]-phenyl}-2-chlorobenzenesulfonamide;
N-methyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a] pyrimidin-7-yl]-phenyl}-3-chlorobenzenesulfonamide;
N-methyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a] pyrimidin-7-yl]-phenyl}-4-chlorobenzenesulfonamide;
N-methyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a] pyrimidin-7-yl]-phenyl}-2,4-dichlorobenzene-sulfonamide;
N-methyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a] pyrimidin-7-yl]-phenyl}-3,4-dichlorobenzene-sulfonamide;
N-methyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a] pyrimidin-7-yl]-phenyl}-2-cyanobenzenesulfonamide;
N-methyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a] pyrimidin-7-yl]-phenyl}-3-cyanobenzenesulfonamide;
N-methyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a] pyrimidin-7-yl]-phenyl}-4-cyanobenzenesulfonamide;

N-methyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a] pyrimidin-7-yl]-phenyl}-3-nitrobenzenesulfonamide;
N-methyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a] pyrimidin-7-yl]-phenyl}-4-nitrobenznesulfonamide;
N-methyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a] pyrimidin-7-yl]-phenyl}-2-thiophenesulfonamide;
N-methyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a] pyrimidin-7-yl]-phenyl}-5-methyl-4-isoxazolyl-sulfonamide;
N-methyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a] pyrimidin-7-yl]-phenyl}-2-trifluoromethyl-5-methyl-3-furylsulfonamide;
N-methyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a] pyrimidin-7-yl]-phenyl}-6-(morpholin-4-yl)-3-pyridylsulfonamide;
N-methyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a] pyrimidin-7-yl]-phenyl}-2,4-dimethyl-5-thiazolyl-sulfonamide;
N-methyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a] pyrimidin-7-yl]-phenyl}-cyclopropylsulfonamide;
N-methyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a] pyrimidin-7-yl]-phenyl}-benzylsulfonamide;
N-methyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a] pyrimidin-7-yl]-phenyl}-vinylsulfonamide;
N-methyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a] pyrimidin-7-yl]-phenyl}-3,5-dimethyl-4-isoxazolyl-sulfonamide;
N-methyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a] pyrimidin-7-yl]-phenyl}-1,3,5-trimethyl-4-pyrazolyl-sulfonamide;
N-methyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a] pyrimidin-7-yl]-phenyl}-propanesulfonamide;
N-methyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a] pyrimidin-7-yl]-phenyl}-butanesulfonamide;

N-methyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a] pyrimidin-7-yl]-phenyl}-cyclopentylmethane-sulfonamide;
N-{3-[3-(5-methyl-[1,2,4]oxadiazol-3-yl)-pyrazolo[1,5-a] pyrimidin-7-yl]-phenyl}-methanesulfonamide; and
N-ethyl-N-{3-[3-(5-methyl-[1,2,4]oxadiazol-3-yl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-methanesulfonamide.

Another embodiment of the present invention is to provide a process for preparing the compounds of formula (I) and their pharmaceutically acceptable salts.

Another embodiment of the present invention is to provide a method for treating or preventing diseases associated with $GABA_A$ receptor modulation in a mammal which comprises administering to said mammal an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

Another embodiment of the present invention is to provide a method for treating or preventing diseases associated with α_1-$GABA_A$ receptor modulation in a mammal which comprises administering to said mammal an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

Another embodiment of the present invention is to provide a method for treating or preventing diseases associated with α_2-$GABA_A$ receptor modulation in a mammal which comprises administering to said mammal an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

Another embodiment of the present invention is to provide a method for treating or preventing anxiety in a mammal which comprises administering to said mammal an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

Another embodiment of the present invention is to provide a method for treating or preventing epilepsy in a mammal which comprises administering to said mammal an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

Another embodiment of the present invention is to provide a method for treating or preventing sleep disorders in a mammal which comprises administering to said mammal an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

Another embodiment of the present invention is to provide a method for treating or preventing insomnia in a mammal which comprises administering to said mammal an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

Another embodiment of the present invention is to provide a method for inducing sedation-hypnosis in a mammal which comprises administering to said mammal an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

Another embodiment of the present invention is to provide a method for inducing anesthesia in a mammal which comprises administering to said mammal an effective amount of a

compound of formula (I) or a pharmaceutically acceptable salt thereof.

Another embodiment of the present invention is to provide a method for modulating the necessary time to induce sleep and its duration in a mammal which comprises administering to said mammal an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

Another embodiment of the present invention is to provide a method for inducing muscle relaxation in a mammal which comprises administering to said mammal an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

Another embodiment of the present invention is to provide a pharmaceutical composition containing a compound of formula (I) or a pharmaceutically acceptable salt thereof in association with therapeutically inert carriers.

The compositions include those suitable for oral, rectal and parenteral (including subcutaneous, intramuscular, and intravenous) administration, although the most suitable route will depend on the nature and severity of the condition being treated. The most preferred route of the present invention is the oral route. The compositions may be conveniently presented in unit dosage form, and prepared by any of the methods well known in the art of pharmacy.

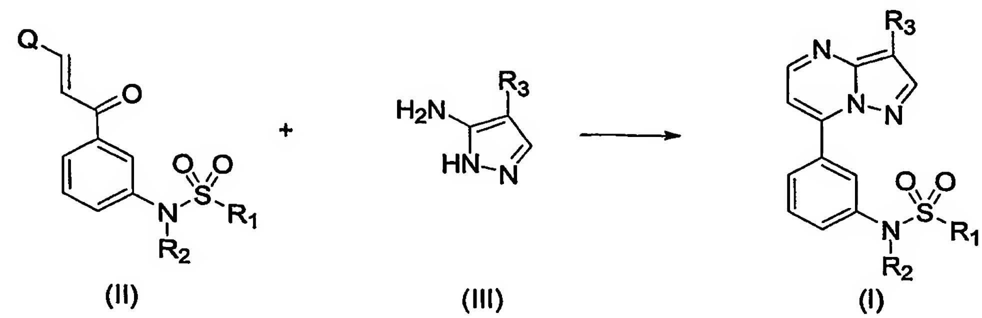
The active compound can be combined with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques. The carrier may take a wide variety of

forms depending on the form of the preparation desired for administration, e.g. oral or parenteral (including intravenous injections or infusions). In preparing the compositions for oral dosage form any of the usual pharmaceutical media may be employed. Usual pharmaceutical media include, for example, water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents, and the like in the case of oral liquid preparations (such as for example, suspensions, solutions, emulsions and elixirs); aerosols; or carriers such as starches, sugars, microcrystalline cellulose, diluents, granulating agents, lubricants, binders, disintegrating agents and the like, in the case of oral solid preparations (such as for example, powders, capsules, and tablets) with the oral solid preparations being preferred over the oral liquid preparations.

Because of their ease of administration, tablets and capsules represent the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are employed. If desired, tablets may be coated by standard aqueous or nonaqueous techniques.

A suitable dosage range for use is from about 0.01 mg to about 100,00 mg total daily dose, given as a once daily administration or in divided doses if required.

The compounds of general formula (I) may be prepared according to the reaction shown in Scheme 1.

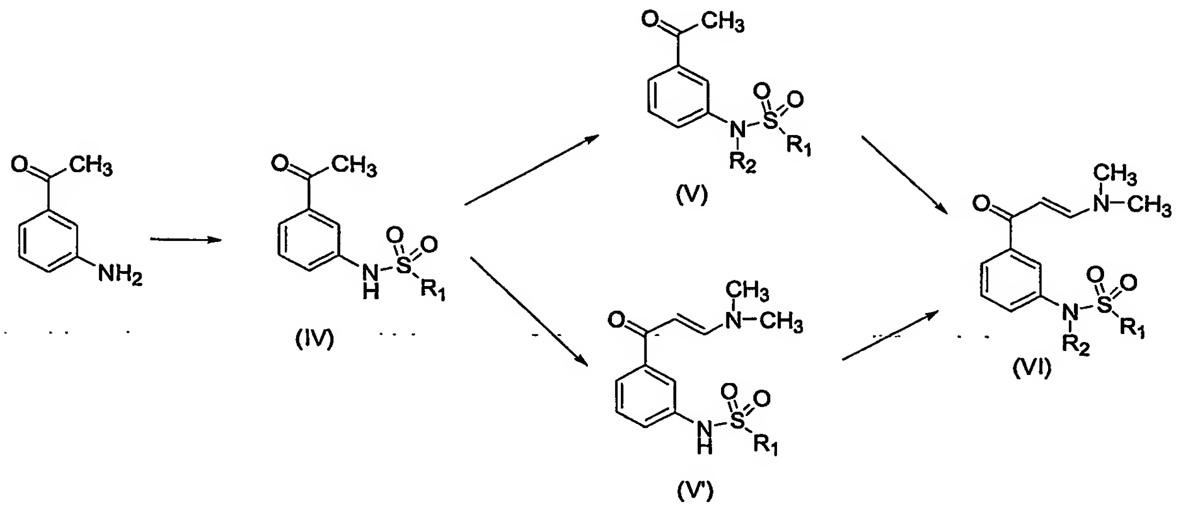


Scheme 1

R_1, R_2 and R_3 are as described above and Q is an appropriate leaving group consisting of N(dialkyl(C_1-C_6)), alkylthio(C_1-C_6) and alkoxy(C_1-C_6). Preferably Q is selected from the group consisting of dimethylamino, methylthio or methoxy.

The reaction of aminopyrazole of general formula (III) with appropriately substituted 1-aryl-2-propen-1-one (II) is carried out in an inert polar protic or aprotic solvent such as glacial acetic acid, ethanol, methanol, dimethylformamide or dimethylsulfoxide at a temperature ranging from 50° to 130°C. After elapsing several hours (reaction time), the solvent is removed and the residue obtained is partitioned between an aqueous solution of sodium bicarbonate and dichloromethane. The crude resulting from evaporating the organic layer to dryness may be purified by one of the following methods: (a) silica gel chromatography using ethyl acetate or dichloromethane /methanol as eluent; or (b) crystallization in a suitable solvent (ethyl acetate, ethanol, methanol, etc.).

The intermediate of formula (II) when Q is dimethylamino [intermediate (VI)] can be obtained following the reaction sequence shown in Scheme 2



Scheme 2

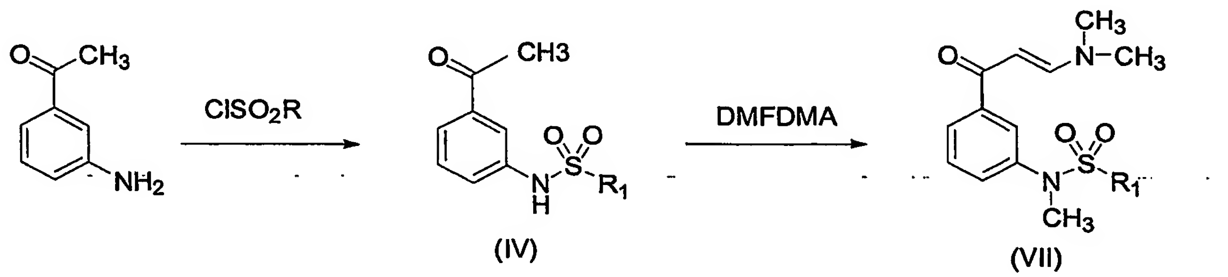
wherein R_1 and R_2 are as described above.

The sulfonamides of formula (IV) are prepared according to the method described by R. H. Uloth et al (J. Med. Chem. 9, 88-96, 1966).

The alkylation of the sulfonamides (IV) leading to the intermediates of formula (V) is performed, in accordance with methods well known by experts in Organic Chemistry, via formation of an anion and subsequent reaction with an alkyl halide.

The enaminones of formula (VI) are prepared according to general synthetic procedures of enamines described by J. M. Domagala et al (J. Heterocyclic Chem., 26(4), 1147-58, 1989); and K. Sawada et al (Chem. Pharm. Bull., 49(7), 799-813, 2001) by reacting an acetophenone with N,N-dimethylformamide dimethylacetal (DMFDMA) or Bredereck's reagent (*tert*-butoxybis(dimethylamino)methane).

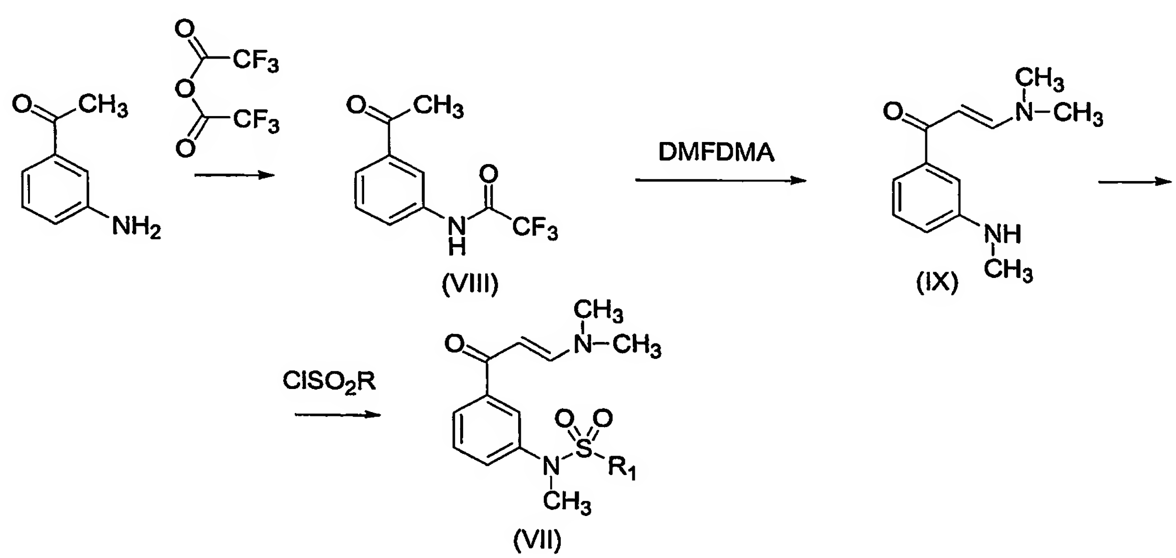
The intermediates of formula (II), when Q is dimethylamino and R_2 is methyl (VII), can alternatively be prepared according to Scheme 3.



Scheme 3

The conversion of (IV) into (VII) leads to the formation of the enaminone and, simultaneously, the formation of the N-methyl-sulfonamide as a result of the use of the properties of the N,N-dimethylformamide dimethyl acetal as a methylating agent.

Intermediate (VII) can also be prepared according to Scheme 4.



Scheme 4

The advantage of this process is based on the fact that the formation of the sulfonamide takes place in the last state of process. As a result, the total number of reaction steps is reduced in the preparation of large series of products. Moreover, as shown in the scheme, the conversion of (VIII) into (IX) leads to three following reactions in a one-pot process: (a) formation of the anaminone; (b) methylation of the trifluoroacetamide; and (c) deacylation yielding the N-methylated amine. The subsequent reaction of (IX) with the corresponding sulfonic acid chloride leads to obtaining intermediates (VII).

The preparation of intermediates (VII) by reaction between intermediates (IV) and N,N-dimethylformamide dimethyl acetal has not ever disclosed in the chemical literature and is another embodiment of the present invention.

Similarly, the preparation of intermediates (VII) by reaction between N-(3-acetylphenyl)-2,2,2-trifluoro-acetamide (VIII) and N,N-dimethylformamide dimethyl acetal, followed by the formation of the sulfonamide by reaction with the corresponding sulfonic acid chloride have not disclosed either in the chemical literature and is another embodiment of the present invention.

From the compounds of general formula (I) it is possible to obtain their pharmaceutically acceptable salts by treatment with the corresponding acids.

The applicants have discovered that the compounds of the present invention have a high affinity for α_1- and α_2-$GABA_A$ receptors as shown in Tables 1 and 2. These *in vitro*

results are consistent with those *in vivo* results obtained in sedation-hypnosis tests (Table 3).

In accordance with the results obtained, certain compounds of the present invention have surprisingly evidenced pharmacological activity both *in vitro* and *in vivo*, which has been similar to or higher than that of prior-art compounds. All these results support their use in diseases or conditions modulated by α_1- and α_2-$GABA_A$ receptors, such as insomnia or anesthesia, in which an induction of sleep, an induction of sedation or an induction of muscle relaxation are needed.

The pharmacological activity of the compounds of the present invention has been determined as shown below.

Ligand-binding assays. Determination of the affinity of test compounds for α_1- and α_2-$GABA_A$ receptor.

Male Sprague-Dawley rats weighing 200-250 g at the time of experiment were used. After decapitation of the animal, the cerebellum (tissue that mostly contains α_1-$GABA_A$ receptor) and spinal cord (tissue that mostly contains α_2-$GABA_A$ receptor) were removed. The membranes were prepared according to the method by J. Lameh et al.(Prog. Neuro-Psychopharmacol. Biol. Psychiatry, 24, 979-991, 2000). Once the tissues weighed, they were suspended in 50 mM Tris·HCl (pH 7.7), 1:40 (v/v), homogenized and then centrifuged at 20000 g for 10 min at 7°C. The resulting pellet was resuspended under the same conditions and centrifuged again. The pellet was finally resuspended on a minimum volume and kept at -80°C overnight. On the next day, the

process was repeated until the final pellet was resuspended at a ratio of 1:10 (v/v).

Affinity was determined by competitive tests using radiolabeled flumazenil as ligand. The tests were performed according to the methods described by S. Arbilla et al. (Eur. J. Pharmacol., 130, 257-263, 1986); and Y. Wu et al. (Eur. J. Pharmacol., 278, 125-132, 1995). The membranes containing the study receptors, flumazenil (radiolabeling at a final concentration of 1 nM) and ascending concentrations of test compounds (in a total volume of 500 µl in 50 nM [ph 7.4] Tris·HCl buffer) were incubated. Simultaneously, the membranes were only incubated with the radiolabeled flumazenil (total binding, 100%) and in the presence of an elevated concentration of unradiolabeled flumazenil (non-specific binding, % estimation of radiolabeled ligand). The reactions started on adding the radiolabeled ligand followed by incubation for 60 minutes at 0°C. At the end of the incubation period, the tubes were filtered using a Brandel Mod. M-48R harvester and then washed three times with cold test buffer. The harvester was fitted with a GF/B filter that retained the membranes containing the receptors and the radiolabeled ligand which had been bound to the receptors. Then the filters were removed and left till dry. Once dried, the filters were cut, placed in vials with scintillation liquid and left under stirring overnight. The next day the filters were counted using a Packard Mod. Tricarb scintillation counter. For analysis of the results the percentage of specific binding for every concentration of test compound was calculated as follows:

$$\% \text{ specific binding} = (X-N/T-N) \times 100$$

where,

X: amount of bound ligand for every concentration of compound.

T: total binding, maximum amount bound to the radiolabeled ligand.

N: non-specific binding, amount of radiolabeled ligand bound in a non-specific way irrespective of the receptor used.

Every concentrations of compound were tested in duplicate and their mean values were used to determine the experimental values of % specific binding versus the concentration of compound. The values thus attained were fitted to a equation for competitive assays (SigmaPlot, SPSS Inc.) and the IC_{50} values (concentration of compound able to inhibit by 50% the specific binding). Inhibition constants (K_i) were calculated from the IC_{50} values according to Cheng-Prusoff's formula (Y. Cheng y W. H. Prusoff, Biochem. Pharmacol., 22(23), 3099-3108, 1973). The affinity data for subunit α_2 are alternatively expressed as % inhibition at the concentrations of 10^{-5} M and 10^{-7} M. The results of these tests are given in Tables 1 and 2.

Table 1. Affinity for α_1-$GABA_A$ receptor

Compound	Ki (nM)
Example 2	74.5
Example 3	7.4
Example 5	13.4
Example 6	3.0
Example 16	0.7
Example 17	28.0
Example 18	5.9
Example 19	0.5
Example 20	12.5
Example 22	20.9
Example 23	26.7

Example 24	30.7
Example 25	26.6
Example 27	28.2
Example 29	53.2
Example 30	52.1
Example 33	608.7
Example 34	33.2
Example 35	88.9
Example 37	577.8
Example 38	119.4
Example 39	37.2
Example 40	7.3
Example 46	41.0
Example 51	38.7
Example 52	48.1
Example 53	33.2
Example 58	47.9
Example 63	62.1
Example 64	32.9
Example 68	8.9
Example 69	16.6
Example 70	6.2
Example 72	14.6
Example 76	201.2
Example 77	35.6
Example 78	2031.0
Example 79	499.0
Example 82	63.6
Example 83	42.0
Example 84	28.9
Example 87	1.9
Example 91	2.8
Example 92	0.4
Example 94	0.5
Zaleplon	198.9

Table 2. Affinity for α_2-$GABA_A$ receptor

Compound	K_i (nM)
Example 2	831.3
Example 3	36.7
Example 5	290.2

Example 6	34.9	
Zaleplon	1302.5	
Compound	% Inhibition (10^{-5}M)	% Inhibition (10^{-7}M)
Example 16	100.2	87.2
Example 17	74.5	0
Example 18	93.7	20.7
Example 19	94.4	45.2
Example 20	97.7	40.3
Example 22	98.2	24.2
Example 23	93.8	45.5
Example 24	83.0	10.4
Example 25	78.9	9.1
Example 27	85.2	2.9
Example 29	92.7	13.4
Example 30	73.3	0
Example 33	45.2	0
Example 34	87.6	6.9
Example 35	86.5	24.5
Example 37	40.2	0
Example 38	77.6	17.4
Example 39	96.6	23.3
Example 40	99.5	47.3
Example 46	97.6	11.9
Example 51	94.7	16.8
Example 52	61.2	0
Example 53	89.8	1.0
Example 58	93.8	24.0
Example 63	91.3	0
Example 64	61.5	20.9
Example 68	92.7	31.6
Example 69	99.0	36.7
Example 70	99.9	63.4

Example 72	98.6	44.9
Example 76	41.7	0
Example 77	88.5	13.8
Example 78	36.2	0
Example 79	52.9	0
Example 82	31.8	0
Example 83	94.4	39.1
Example 84	89.5	0
Example 87	97.6	65.1
Example 91	84.1	4.8
Example 92	95.7	36.5
Example 94	99.5	41.2
Zaleplon	78.4	--

In vivo determination of predictive sedative-hypnotic action.

The *in vivo* effects of these compounds were assessed by a predictive sedation-hypnosis test in mice (D. J. Sanger et al., Eur. J. Pharmacol., 313, 35-42, 1996; and G. Griebel et al., Psychopharmacology, 146, 205-213, 1999).

Groups of 5-8 male CD1 mice, weighing 22-26 g at the time of test, were used. The test compounds were administered in single equimolecular intraperitoneal doses, suspended in 0.25% agar with one drop of Tween in a volume of 10 ml/kg. Control animals received the vehicle alone. Using an Actisystem DAS16 (Panlab, S.L., Spain) the crossings (number of counts) were recorded for each mouse at 5-min intervals during a period of 30 minutes after dosing. The inhibition percentage of crossings of treated animals versus control animals (the first 5 min were discarded) was calculated. The results of this test are given in Table 3.

Table 3. Determination of sedation-hypnosis in mice.

Compound	% Motor Activity Inhibition
Example 2	71.39
Example 3	93.58
Example 5	80.91
Example 6	66.55
Example 16	95.36
Example 17	94.21
Example 18	93.39
Example 19	89.88
Example 20	95.23
Example 22	91.39
Example 23	94.57
Example 24	94.01
Example 25	92.79
Example 27	93.12
Example 29	93.73
Example 30	94.86
Example 33	77.58
Example 34	92.58
Example 35	92.55
Example 37	92.13
Example 38	94.85
Example 39	95.28
Example 40	94.32
Example 46	93.98
Example 51	90.04
Example 52	92.83
Example 53	94.89
Example 58	93.31
Example 63	95.32

Example 64	90.32
Example 68	87.78
Example 69	96.90
Example 70	94.54
Example 72	93.78
Example 76	78.36
Example 77	70.12
Example 78	36.12
Example 79	51.50
Example 82	39.87
Example 83	53.38
Example 84	68.98
Example 87	74.88
Example 91	72.85
Example 92	74.36
Example 94	88.69
Zaleplon	47.17

The following non-limiting examples illustrate the scope of the present invention.

Example 1: N-[3-[3-(dimethylamino)-1-oxo-2-propenyl] phenyl]-N-methyl-methanesulfonamide

1.58 g (6.96 mmol) of N-(3-acetyl-phenyl)-N-methyl-methanesulfonamide were dissolved in 15 ml of N,N-dimethylformamide dimethylacetal and the resultant solution was refluxed for 18 hours. The excess of volatile reagent was removed by reduced pressure distillation to yield a crude which was chromatographied over silica gel using a gradient of ethyl acetate/methanol as eluent. 1.12 g of N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-N-methyl

methanesulfonamide as a yellowish-white solid were obtained (yield 88.6%).

^{1}H NMR(400 MHz, DMSO-d_6): δ 2.91 (3H, s), 2.94 (3H, s), 3.14 (3H, s), 3.26 (3H, s), 5.79 (1H, d, J= 12.4 Hz), 7.44 (1H, t, J= 7.6 Hz), 7.49-7.52 1H, m), 7.71 (1H, d, J= 12.4 Hz), 7.78-7.81 (2H, m).
MS (ES) *m/z* = 283 (MH+)
HPLC = 99.2%

Example 2: N-[3-(3-cyano-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-N-methyl-methanesulfonamide

A mixture of 0.1 g (0.93 mmol) of 4-cyano-2H-pyrazol-3-ylamine and 0.26 g (0.93 mmol) of N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-N-methyl-methanesulfonamide in 10 ml of glacial acetic acid was refluxed for 8 hours and then the solvent was removed by reduced pressure distillation. To the resulting residue were added 10 ml of dichloromethane and 10 ml of saturated sodium bicarbonate solution. The two layers were separated, and the aqueous layer was washed with 10 ml of dichloromethane. The organic layers were washed with 10 ml of water and dried over magnesium sulfate. The dichloromethane layer was evaporated to dryness to yield an oil which, in the presence of ethyl acetate, gave 217 mg of N-[3-(3-cyano-pyrazolo[1,5-a] pyrimidin-7-yl)-phenyl]-N-methyl-methanesulfonamide as a yellow solid (yield 71%; m.p.= 193-195 °C).

^{1}H NMR(400 MHz, DMSO-d_6): δ 3.01 (3H, s,), 3.30 (3H, s), 7.60 (1H, d, J= 4.8 Hz), 7.65-7.67 (2H, m), 8.00-8.02 (1H, m), 8.09 (1H, s), 8.85 (1H, s), 8.91 (1H, d, J= 4.8 Hz).
MS (ES) *m/z* = 328 (MH+)

HPLC = 95.9%

Example 3: N-methyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo [1,5-a]pyrimidin-7-yl]-phenyl}-methanesulfonamide

A mixture of 0.1 g (0.52 mmol) of (5-amino-1H-pyrazol-4-yl)-thiophene-2-yl-methanone and 0.146 g (0.93 mmol) of N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-N-methyl-methanesulfonamide (obtained as described in Example 2) in 10 ml of glacial acetic acid was refluxed for 8 hours and then the solvent was removed by reduced pressure distillation. To the resulting residue were added 10 ml of dichloromethane and 10 ml of saturated sodium bicarbonate solution. The two layers were separated, and the aqueous layer was washed with 10 ml of dichloromethane. The organic layers were washed with 10 ml of water and dried over magnesium sulfate. The dichloromethane layer was evaporated to dryness to yield an oil which, in the presence of ethyl acetate, gave 178 mg N-methyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-methane-sulfonamide as a yellow solid (yield 83%; m.p. = 169-170°C).

^{1}H NMR(400 MHz, DMSO-d_6): δ 3.02 (3H, s,), 3.32 (3H, s), 7.29 (1H, t, J= 6 Hz), 7.54 (1H, d, J= 4.4 Hz), 7.62-7.67 (2H, m), 8.02-8.04 (2H, m), 8.11 (1H, s), 8.20 (1H, d, J= 6 Hz), 8.80 (1H, s), 8.89 (1H, d, J= 4.4 Hz).
MS (ES) *m/z* = 413 (MH+)
HPLC = 99.2%

Example 4: N-[3-[3-(dimethylamino)-1-oxo-2-propenyl] phenyl]-N-ethyl-methanesulfonamide

1.1 g (4.56 mmol) of N-(3-acetyl-phenyl)-N-ethyl-methanesulfonamide were dissolved in 10 ml of N,N-dimethylformamide dimethylacetal and the resultant solution was refluxed for 18 hours. The excess of volatile reagent was removed by reduced pressure distillation to yield a crude which was chromatographied over silica gel using a gradient of ethyl acetate/methanol as eluent. 1.2 g of N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-N-ethyl-methanesulfonamide as a yellowish-white solid were obtained (yield 88.6%)

^{1}H NMR(400 MHz, $CDCl_3$): δ 1.23 (3H, t, J= 7.2 Hz), 2.88 (3H, s), 2.94 (3H, s), 3.16 (3H, s), 3.76 (2H, q, J= 7.2 Hz), 5.66 (1H, d, J= 12 Hz), 7.41-7.44 (2H, m), 7.79 (1H, d, J= 12 Hz), 7.80-7.84 (2H, m).
HPLC = 95.6%

Example 5: N-[3-(3-cyano-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-N-ethyl-methanesulfonamide

A mixture of 0.196 g (1.82 mmol) of 4-cyano-2H-pyrazol-3-ylamine and 0.54 g (1.82 mmol) of N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-N-ethyl-methanesulfonamide in 10 ml of glacial acetic acid was refluxed for 8 hours and then the solvent was removed by reduced pressure distillation. To the resulting residue were added 10 ml of dichloromethane and 10 ml of saturated sodium bicarbonate solution. The two layers were separated, and the aqueous layer was washed with 10 ml of dichloromethane. The organic layers were washed with 10 ml of water and dried over magnesium sulfate. The dichloromethane layer was evaporated to dryness to yield an oil which, in the presence of ethyl acetate, gave 324 mg of N-[3-(3-cyano-pyrazolo[1,5-

a]pyrimidin-7-yl)-phenyl]-N-ethyl-methanesulfonamide as a yellow solid (yield 52.4%).

^{1}H NMR(400 MHz, $CDCl_3$): δ 1.21 (3H, t, J= 7.2 Hz), 2.95 (3H, s), 3.81 (2H, q, J= 6.8 Hz), 7.21 (1H, d, J= 4.4 Hz), 7.58-7.60 (1H, m), 7.64 (1H, t, J= 7.6 Hz), 7.98 (1H, d, J= 7.2 Hz), 8.06 (1H, s), 8.41 (1H, s), 8.78 (1H, d, J= 4 Hz).
MS (ES) *m/z* = 342 (MH+)
HPLC = 98.9%

Example 6: N-ethyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo [1,5-a]pyrimidin-7-yl]-phenyl}-methanesulfonamide

A mixture of 0.36 g (1.86 mmol) of 5-amino-1H-pyrazol-4-yl)-thiophene-2-yl-methanone and 0.55 g (1.86 mmol) of N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-N-ethyl-methane sulfonamide in 10 ml of glacial acetic acid was refluxed for 8 hours. Thereafter, the reaction mixture was cooled and the precipitate formed, which was filtered, was washed first with acetic acid, then with saturated sodium bicarbonate solution and finally with water. 472 mg of N-ethyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a] pyrimidin-7-yl]-phenyl}-methane-sulfonamide were obtained as a yellow solid (yield 59.6%).

^{1}H NMR(400 MHz, $CDCl_3$): δ 1.23 (3H, t, J= 7.6 Hz), 2.97 (3H, s), 3.82 (2H, q, J= 6.8 Hz), 7.17 (1H, d, J= 4.4 Hz), 7.18-7.20 (1H, m), 7.57-7.60 (2H, m), 7.62 (1H, t, J= 7.2 Hz), 7.69 1H, dd, J= 4.8 y 1.2 Hz), 7.99-8.02 (1H, m), 8.07-8.1 (3H, m), 8.69 (1H, s), 8.80 (1H, d, J= 4.4 Hz).
MS (ES) *m/z* = 427 (MH+).

HPLC = 98.3%

Example 7: N-[3-[3-(dimethylamino)-1-oxo-2-propenyl] phenyl]-N-methyl-benzenesulfonamide

1.25 g (4.32 mmol) of N-(3-acetyl-phenyl)-N-methyl-benzenesulfonamide were dissolved in 10 ml of N,N-dimethylformamide dimethylacetal and the resultant solution was refluxed for 18 hours. The excess of volatile reagent was removed by reduced pressure distillation to yield a crude which was chromatographied over silica gel using a gradient of ethyl acetate/methanol as eluent. 1.25 g of N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-N-methyl-benzenesulfonamide as a yellowish-white solid were obtained (yield 84%).

^{1}H NMR(400 MHz, $CDCl_3$): δ 2.92 (3H, s), 3.15 (3H, s), 3.19 (3H, s), 5.58 (1H, d, J= 12 Hz), 7.21-7.23 (1H, m), 7.33 (1H, t, J= 8 Hz), 7.41-7.46 (2H, m), 7.52-7.58 (4H, m), 7.76 (1H, d, J=12 Hz), 7.77-7.80 (1H, m).
HPLC = 100%

Example 8: N-[3-(3-cyano-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-N-methyl-benzenesulfonamide

A mixture of 0.134 g (1.24 mmol) of 4-cyano-2H-pyrazol-3-ylamine and 0.43 g (1.24 mmol) of N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-N-methyl-benzenesulfonamide in 10 ml of glacial acetic acid was refluxed for 8 hours and then the solvent was removed by reduced pressure distillation. To the resulting residue were added 10 ml of dichloromethane and 10 ml of saturated sodium bicarbonate solution. The two layers were separated, and the aqueous

layer was washed with 10 ml of dichloromethane. The organic layers were washed with 10 ml of water and dried over magnesium sulfate. The dichloromethane layer was evaporated to dryness to yield an oil which, in the presence of ethyl acetate, gave 205 mg of N-[3-(3-cyano-pyrazolo[1,5-a] pyrimidin-7-yl)-phenyl]-N-methyl-benzenesulfonamide as a yellow solid (yield 42%).

^{1}H NMR(400 MHz, $CDCl_3$): δ 3.23 (3H, s,) 7.13 (1H, d, J= 4.8 Hz), 7.25-7.30 (1H, m), 7.45-7.63 (6H, m), 7.83 (1H, s), 7.93-7.97 (1H, m), 8.37 (1H, s), 8.75 (1H, d, J= 4.4 Hz).
MS (ES) *m/z* = 390 (MH+)
HPLC = 99.0%

Example 9: N-methyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo [1,5-a]pyrimidin-7-yl]-phenyl}-benzenesulfonamide

A mixture of 0.43 g (2.23 mmol) of (5-amino-1H-pyrazol-4-yl)-thiophene-2-yl-methanone and 0.8 g (2.23 mmol) of N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-N-methyl-methane-sulfonamide in 10 ml of glacial acetic acid was refluxed for 8 hours and then the solvent was removed by reduced pressure distillation. To the resulting residue were added 10 ml of dichloromethane and 10 ml of saturated sodium bicarbonate solution. The two layers were separated, and the aqueous layer was washed with 10 ml of dichloromethane. The organic layers were washed with 10 ml of water and dried over magnesium sulfate. The dichloromethane layer was evaporated to dryness to yield an oil which, in the presence of ethyl acetate, gave 872 g of N-methyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]

pyrimidin-7-yl]-phenyl}-benzenesulfonamide as a yellow solid (yield 82.3%).

^{1}H NMR(400 MHz, $CDCl_3$): δ 3.24 (3H, s), 7.07 (1H, d, J= 4.4 Hz), 7.19 (1H, t, J= 4 Hz), 7.28-7.31 (1H, m), 7.46-7.62 (6H, m), 7.7 (1H, d, J= 5.2 Hz), 7.82 (1H, t, J= 2 Hz), 7.97 (1H, d, J= 6.8 Hz), 8.09 (1H, d, J= 3.6 Hz), 8.66 (1H, s), 8.79 (1H, d, J= 4.4 Hz).
MS (ES) *m/z* = 475 (MH+)
HPLC = 97.9%

Example 10: N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-N-ethyl-benzenesulfonamide

1.05 g (3.46 mmol) of N-(3-acetyl-phenyl)-N-ethyl-benzenesulfonamide were dissolved in 10 ml of N,N-dimethylformamide dimethylacetal and the resultant solution was refluxed for 18 hours. The excess of volatile reagent was removed by reduced pressure distillation to yield a crude which was chromatographied over silica gel using a gradient of ethyl acetate/methanol as eluent. 1.2 g of N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-N-ethyl-benzenesulfonamide as a yellowish-white solid were obtained (yield 96%).

^{1}H NMR(400 MHz, $CDCl_3$): δ 1.06 (3H, t, J= 7.2 Hz), 2.92 (3H, s), 3.15 (3H, s), 3.62 (2H, q, J= 7.6 Hz), 5.56 (1H, d, J= 12.4 Hz), 7.14-7.17 (1H, m), 7.35 (1H, t, J= 7.6 Hz), 7.42-7.49 (3H, m), 7.52-7.60 (3H, m), 7.76 (1H, d, J=12.4 Hz), 7.81 (1H, d, J= 8 Hz).
HPLC = 100%

Example 11: N-[3-(3-cyano-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-N-ethyl-benzenesulfonamide

A mixture of 0.15 g (1.38 mmol) of 4-cyano-2H-pyrazol-3-ylamine and 0.50 g (1.38 mmol) of N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-N-ethyl-benzenesulfonamide in 10 ml of glacial acetic acid was refluxed for 8 hours and then the solvent was removed by reduced pressure distillation. To the resulting residue were added 10 ml of dichloromethane and 10 ml of saturated sodium bicarbonate solution. The two layers were separated, and the aqueous layer was washed with 10 ml of dichloromethane. The organic layers were washed with 10 ml of water and dried over magnesium sulfate. The dichloromethane layer was evaporated to dryness to yield an oil which, in the presence of ethyl acetate, gave 260 mg of N-[3-(3-cyano-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-N-ethyl-benzenesulfonamide as a yellow solid (yield 47%).

^{1}H NMR(400 MHz, $CDCl_3$): δ 1.14 (3H, t, J= 6.8 Hz), 3.66 (2H, q, J= 7.2 Hz), 7.12 (1H, d, J= 4.8 Hz), 7.26 (1H, d, J= 7.6 Hz), 7.46-7.65 (6H, m), 7.76 (1H, s), 8.02 (1H, d, J= 7.6 Hz), 8.38 (1H, s), 8.76 (1H, d, J= 4.4 Hz).
MS (ES) *m/z* = 404 (MH+)
HPLC = 98.9%

Example 12: N-ethyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo [1,5-a]pyrimidin-7-yl]-phenyl}-benzenesulfonamide

A mixture of 0.33 g (1.70 mmol) of (5-amino-1H-pyrazol-4-yl)-thiophene-2-yl-methanone and 0.61 g (1.70 mmol) of N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-N-ethyl-benzenesulfonamide in 10 ml of glacial acetic acid was

refluxed for 8 hours and then the solvent was removed by reduced pressure distillation. To the resulting residue were added 10 ml of dichloromethane and 10 ml of saturated sodium bicarbonate solution. The two layers were separated, and the aqueous layer was washed with 10 ml of dichloromethane. The organic layers were washed with 10 ml of water and dried over magnesium sulfate. The dichloromethane layer was evaporated to dryness to yield an oil which, in the presence of ethyl acetate, gave 535 mg of N-ethyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a] pyrimidin-7-yl]-phenyl}-benzenesulfonamide as a yellow solid (yield 64.4%).

^1H NMR(400 MHz, $CDCl_3$): δ 1.15 (3H, t, J= 7.6 Hz), 3.67 (2H, q, J= 7.6 Hz), 7.07 (1H, d, J= 4.4 Hz), 7.18-7.21 (1H, m), 7.27-7.30 (1H, m), 7.51 (2H, t, J= 7.6 Hz), 7.56 (1H, t, J= 7.6 Hz), 7.60-7.67 (4H, m), 7.69 (1H, dd, J= 5.2 Hz y J= 1.2 Hz), 7.75 (1H, t, J= 2 Hz), 8.06 (1H, d, J= 7.6 Hz), 8.09 (1H, d, J= 3.6 Hz), 8.67 (1H, s), 8.79 (1H, d, J= 4.4 Hz).
MS (ES) *m/z* = 489 (MH+)
HPLC = 97.9%

Example 13: General procedure for the preparation of N-methyl-enamine-sulfonamides of general formula (VI) following Scheme 2

N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-N-ethyl-ethanesulfonamide

2 g (8.8 mmol) of N-(3-acetyl-phnyl)-ethanesulfonamide were dissolved in 15 ml of N,N-dimethylformamide dimethyl acetal

and heated at 150°C for 12 h. The solvent was removed by reduced pressure distillation to yield a crude which was chromatographied (silica gel) using ethyl acetate/methanol as eluent. 1.4 g (yield= 56%) of N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-ethanesulfonamide were obtained.

0.25 g (0.89 mmol) of N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-ethanesulfonamide were dissolved inn 6 ml of dry N,N-dimethylformamide. To the solution formed at 0°C and under inert atmosphere, 0.043 g (1.08 mmol)of sodium hydride were added. After stirring for 30 minutes, 0.15 g (0.98 mmol) of ethyl iodide were added and stirring was maintained at room temperature for 5 h. To the reaction mixture 1 ml of water and then 20 ml of 0.5M NaOH were added. The product was separated by extraction with 3x25 ml of dichloromethane, and the organic layers were washed with 25 ml of water, dried over anhydrous sodium sulfate, filtered off and evaporated to dryness by reduced pressure distillation. 0.25 g (yield= 90%) of N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-N-ethyl-ethane-sulfonamide were obtained as an oil.
^{1}H NMR (400 MHz, $CDCl_3$): δ 1.12 (3H, t, J= 6.8 Hz), 1.37 (3H, t, J= 7.6 Hz), 2.94 (3H, s), 3.01 (2H, q, J= 7.6 Hz), 3.15 (3H, s), 4.79 (2H, q, J= 8.2 Hz), 5.66 (1H, d, J= 12.4 Hz), 7.39-7.46 (2H, m), 7.77-7.84 (3H, m)
HPLC = 99%

As described in the above general procedure, the following compounds were prepared:

N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-N-ethyl-isopropanesulfonamide

^1H NMR (400 MHz, $CDCl_3$): δ 1.12 (3H, t, J= 7.2 Hz), 1.37 (6H, d, J= 6.8 Hz), 2.95 (3H, s), 3.18 (3H, s), 3.18-3.25 (1H, m), 3.82 (2H, q, J= 7.6 Hz), 5.67 (1H, d, J= 12.4 Hz), 7.39-7.49 (2H, m), 7.78-7.81 (2H, m), 7.85-7.87 (1H, m)
HPLC = 99.4%

N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-N-propyl-methanesulfonamide

^1H NMR (400 MHz, DMSO-d_6): δ 0.83 (3H, t, J= 7.6 Hz), 1.31-1.36 (2H, m), 2.49 (3H, s), 2.91 (3H, s), 3.14 (3H, s), 3.61 (2H, t, J= 7.2 Hz), 7.78 (1H, d, J= 12 Hz), 7.42-7.51 (2H, m), 7.71 (1H, d, J= 12.4 Hz), 7.77-7.78 (1H, m), 7.82-7.85 (1H, m)
HPLC = 88.8%

N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-N-propyl-ethanesulfonamide

^1H NMR (400 MHz, $CDCl_3$): δ 0.89 (3H, t, J= 7.6 Hz), 1.37 (3H, t, J= 7.6 Hz), 1.42-1.51 (2H, m), 2.71 (1H, s), 2.94 (3H, s), 3.02 (2H, q, J= 7.6 Hz), 3.16 (3H, s, J= 12.4 Hz), 3.69 (2H, t, J= 7.2 Hz), 7.39-7.47 (2H, m), 7.78-7.85 (3H, m)
HPLC = 98%

N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-N-propyl-isopropanesulfonamide

^1H NMR (400 MHz, $CDCl_3$): δ 0.88 (3H, t, J= 7.2 Hz), 1.37 (6H, d, J= 6.8 Hz), 1.45-1.51 (2H, m), 2.94 (3H, s), 3.17 (3H, s), 3.17-3.24 (1H, m), 3.73 (2H, t, J= 7.6 Hz), 5.67

(1H, d, J= 12.8 Hz), 7.41 (1H, t, J= 8 Hz), 7.48-7.51 (1H, m), 7.77-7.87 (3H, m)
HPLC = 99.6%

N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-N-butyl-methanesulfonamide

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.81 (3H, t, J= 7.6 Hz), 1.25-1.31 (4H, m), 2.92 (3H, s), 3.14 (3H, s), 3.64 (2H, t, J= 6.8 Hz), 5.78 (1H, d, J= 12 Hz), 7.44-7.50 (2H, m), 7.71 (1H, d, J= 12 Hz), 7.76-7.77 (1H, m), 7.82-7.85 (1H, m)
HPLC = 98%

N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-N-butyl-ethanesulfonamide

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.86 (3H, t, J= 7.6 Hz), 1.3-1.46 (7H, m), 2.94 (3H, s), 3.01 (2H, q, J= 7.2 Hz), 3.17 (3H, s), 3.73 (2H, t, J= 7.6 Hz), 5.63 (1H, d), 7.39-7.47 (2H, m), 7.78-7.85 (3H, m)
HPLC = 98.1%

N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-N-butyl-isopropanesulfonamide

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.86 (3H, t, J= 7.6 Hz), 1.28-1.34 (2H, m), 1.36 (6H, d, J= 7.2 Hz), 1.41-1.45 (2H, m), 2.94 (3H, s), 3.16-3.24 (4H, m), 3.76 (2H, t, J= 7.2 Hz), 5.67 (1H, d, J= 12.4 Hz), 7.41 (1H, t, J= 8 Hz), 7.47-7.51 (1H, m).7.78-7.82 (2H, m).7.86-7.88 (1H, m)
HPLC = 99.4%

N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-N-propargyl-methanesulfonamide

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.5 (1H, t, J= 2.8 Hz), 2.94 (3H, s), 3.05 (3H, s), 3.17 (3H, s), 4.46 (2H, s), 5.67 (1H, d, J= 12.4 Hz), 7.44 (1H, t, J= 8 Hz), 7.63-7.66 (1H, m), 7.81 (1H, m, J= 12 Hz), 7.84-7.87 (1H, m).8.09 (1H, t, J= 2 Hz)
HPLC = 98.8%

N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-N-propargyl-ethanesulfonamide

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.39 (3H, t, J= 7.2 Hz), 2.4 (1H, t, J= 2.8 Hz), 2.94 (3H, s), 3.14-3.22 (5H, m), 4.47 (2H, d, J= 2.4 Hz), 5.66 (1H, d, J= 12.4 Hz), 7.42-7.44 (2H, m), 7.61-7.64 (1H, m), 7.78-7.85 (3H, m), 8.05 (1H, t, J= 2 Hz)
MS (ES) m/z = 321 (MH+)

N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-N-propargyl-isopropanesulfonamide

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.4 (6H, d, J= 6.4 Hz), 2.37 (1H, t, J= 2.4 Hz), 2.94 (3H, s), 3.17 (3H, s), 3.34-3.41 (1H, m), 4.49 (2H, d, J= 2.8 Hz), 5.66 (1H, d, J= 12.4 Hz), 7.40-7.44 (1H, m), 7.59-7.62 (1H, m), 7.78-7.87 (2H, m), 7.99-8.00 (1H, m)
HPLC = 81%

Example 14: General procedure for the preparation of N-methyl-enamine-sulfonamides of general formula (VII) following Scheme 3

N-(3-acetylphenyl)-1-propane-sulfonamide

1 g (7.4 mmol) of 3-aminoacetophenone were dissolved in 35 ml of dry dichloromethane. To the resultant solution cooled at 0°C 0.89 ml (11.09 mmol) of anhydrous pyridine and 1.26 g (8.87 mmol) of 1-propanesulfonic acid chloride were added. After stirring the reaction mixture for 20 h at room temperature and under inert atmosphere, 15 ml of water were added. The two layers were separated, and the aqueous layer was washed with 2x15 ml of dichloromethane. The organic layers were washed with 30 ml of water and dried over anhydrous sodium sulfate. The dichloromethane layer was evaporated to dryness to yield a yellow solid, 1.8 g (yield= 100%) of N-(3-acetylphenyl)-1-propane-sulfonamide which was directly used for the following reaction.

N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-N-methyl-1-propanesulfonamide

1 g (4.14 mmol) of N-(3-acetylphenyl)-1-propane-sulfonamide were dissolved in 10 ml of N,N-dimetylformamide. To the resultant solution 2.77 ml (20.74 mmol) of N,N-dimethylformamide dimethyl acetal were added and heated at 150°C for 2 h. The solvent was removed by reduced pressure distillation to yield an oil, which was treated with a mixture of ethyl acetate-ethyl ether.A small quantity of a solid precipitated which was discarded The filtrate was evaporated to dryness, dissolved in dichloromethane, and the organic layer was washed with 4x50 ml of water and

evaporated to dryness. 1.23 g (yield = 96%) of N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-N-methyl-1-propane-sulfonamide were obtained.

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.99 (3H, t, J= 7.6 Hz), 1.75-1.90 (2H, m), 2.91-2.97 (5H, m), 3.15 (3H, a), 3.35 (3H, s), 5.66 (1H, d, J= 12.5 Hz), 7.36-7.52 (2H, m), 7.73-7.88 (3H, m)

As described in the above general procedure, the following compounds were prepared:

N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-N-methyl-butanesulfonamide

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.92 (3H, t, J= 7.4 Hz), 1.35-1.5 (2H, m), 1.75-1.87 (2H, m), 2.97-3.03 (5H, m), 3.18 (3H, a), 3.39 (3H, s), 5.7 (1H, d, J= 12.2 Hz), 7.39-7.46 (1H, m), 7.52-7.56 (1H, m), 7.77-7.87 (1H, m), 7.83 (1H, d, J = 12.2 Hz), 7.9-7.91 (1H, m)

N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-N-methyl-cyclopentylmethanesulfonamide

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.22-1.3 (2H, m), 1.55-1.63 (4H, m), 1.91-1.98 (2H, m), 2.27-2.4 (1H, m), 2.86-2.93 (5H, m), 3.15 (3H, a), 3.34 (3H, s), 5.67 (1H, d, J= 12.5 Hz), 7.37-7.52 (2H, m), 7.44-7.98 (3H, m)

Example 15: General procedure for the preparation of N-methyl-enamine-sulfonamides of general formula (VII) following Scheme 4

N-(3-acetylphenyl)-2,2,2-trifluoroacetamide

5 g (37 mmol) of 3-aminoacetophenone were dissolved in 30 ml of anhydrous dichloromethane. To the resultant solution 3.15 ml (38.84 mmol) of anhydrous pyridine and 5.5 ml (38.84 mmol) of trifluoroacetic anhydride were added at 0°C. The reaction mixture was stirred for 30 minutes at the same temperature and poured onto 100 ml of water-ice.100 ml of a saturated solution of sodium chloride were added and extracted with 2x70 ml of dichloromethane and 3x50 ml of ethyl acetate. The organic layers were washed with water, dried over anhydrous sodium sulfate and evaporated to dryness by reduced pressure distillation. 8.7 g (yield= 100%) as a solid of N-(3-acetylphenyl)-2,2,2-trifluoroacetamide were obtained.

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.64 (3H, s), 7.53 (1H, t, J= 7.6 Hz), 7.82 (1H, d, J= 7.6 Hz), 8.15 (1H, d, J= 8.2 Hz), 8.25 (1H, s), 9.12 (1H, a)

3-(dimetylamino)-1-[3-(methylamino)phenyl]prop-2-en-1-one

8.37 g (36.21 mmol) de N-(3-acetylphenyl)-2,2,2-trifluoroacetamide were dissolved in 80 ml of N,N-dimetyl formamide. To the resultant solution 24.23 ml (181.02 mmol) of N,N-dimethylformamide dimethyl acetal were added and heated at 150°C for 2 h. The solvent was removed by reduced pressure distillation to yield an oil which was treated with 50 ml of water and extract with 3x100 ml of dichloromethane. The organic layers were washed with 2x200 ml of a saturated solution of sodium chloride, dried over anhydrous sodium sulfate and evaporated to dryness by reduced pressure distillation. A solid was obtained, which precipitated from

a mixture of ethanol-ethyl ether to give 4.1 g (yield= 55%) of 3-(dimethylamino)-1-[3-(methylamino)phenyl]prop-2-en-1-one.

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.85 (3H, s), 2.87 (3H, s), 3.11 (3H, s), 3.85 (1H, a), 5.68 (1H, d, J= 12.2 Hz), 6.67-6.72 (1H, m), 7.16-7.24 (3H, m), 7.77 (1H, d, J= 12.2 Hz)

N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-N-metyl-2-phenyl-ethylenesulfonamide

0.4 g (1.96 mmol) of 3-(dimethylamino)-1-[3-(methylamino)phenyl]prop-2-en-1-one were dissolved in 15 ml of dry dichloromethane. To the resultant solution 0.24 ml (2.01 mmol) of anhydrous pyridine and 0.48 g (2.37 mmol) of 2-phenyl-ethene-sulfonic acid chloride were added. After stirring the reaction mixture for 17 h at room temperature and under inert atmosphere, 15 ml of water were added. The two layers were separated, and the aqueous layer was washed with 2x15 ml of dichloromethane. The organic layers were washed with 30 ml of water and dried over anhydrous sodium sulfate. The dicholoromethane layer was evaporated to dryness to yield a crude which was chromatographied (silica gel) using dichloromethane-methanol as eluent. 0.53 (yield= 73%) of a solid, N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-N-methyl-2-phenyl-ethylene-sulfonamide, were obtained

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.9 (3H, a), 3.16 (3H, a), 3.31 (3H, s), 5.65 (1H, d, J= 12.5 Hz), 6.7 (1H, d, J= 15.5 Hz), 7.38-7.5 (8H, m), 7.77-7.85 (3H, m)

As described in the above general procedure the following compounds were prepared:

N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-N-methyl-3-chlorobenzenesulfonamide

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.93 (3H, a), 3.16 (3H, a), 3.22 (3H, s), 5.6 (1H, d), 7.23-7.27 (1H, m), 7.35-7.41 (3H, m), 7.52-7.58 (3H, m), 7.76 (1H, s), 7.79-7.83 (1H, m)

N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-N-methyl-4-chlorobenzenesulfonamide

^{1}H NMR (400 MHz, $CDCl_3$): d 2.94 (3H, a), 3.18 (3H, a), 3.2 (3H, a), 5.59 (1H, d, J= 12.2 Hz), 7.23-7.29 (1H, m), 7.34-7.55 (6H, m), 7.77-7.83 (2H, m)

N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-N-methyl-2-chlorobenzenesulfonamide

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.73 (3H, a), 2.96 (3H, a), 3.24 (3H, s), 5.6 (1H, d, J= 12.5 Hz), 7.06-7.14 (3H, m), 7.21-7.32 (2H, m), 7.5-7.6 (3H, m), 7.68 (1H, dd), J= 7.9 Hz, J= 1.5 Hz)

N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-N-methyl-2,2,2-trifluoroethanesulfonamide

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.95 (3H, a), 3.18 (3H, s), 3.42 (3H, s), 3.73 (2H, c, J= 9.1 Hz), 5.66 (1H, d, J= 12.2 Hz), 7.42-7.53 (2H, m), 7.8 (1H, s), 7.83-7.89 (2H, m)

N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-N-methyl-2,4-dichlorobenzenesulfonamide

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.96 (3H, a), 3.19 (3H, s), 3.46 (3H, s), 5.6 (1H, d, J= 12.2 Hz), 7.27 (1H, d, J= 2.1 Hz), 7.31 (1H, d, J= 1.8 Hz), 7.34-7.38 (1H, m), 7.53 (1H, d, J= 2.1 Hz), 7.71-7.84 (4H, m)

N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-N-methyl-3,4-dichlorobenzenesulfonamide

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.86 (3H, s), 3.09 (3H, s), 3.15 (3H, s), 5.52 (1H, d, J= 12.2 Hz), 7.16-7.23 (1H, m), 7.26 (1H, d, J= 2.1 Hz), 7.32 (1H, t, J= 7.9 Hz), 7.45 (1H, d, J= 8.5 Hz), 7.49 (1H, m), 7.61 (1H, d, J= 2.1 Hz)

N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-N-methyl-2-cyanobenzenesulfonamide

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.97 (3H, a), 3.19 (3H, a), 3.43 (3H, s), 5.64 (1H, d, J= 12.2 Hz), 7.35 (1H, m), 7.41 (1H, t, J= 7.9 Hz), 7.6-7.89 (7H, m)

N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-N-methyl-3-cyanobenzenesulfonamide

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.94 (3H, a), 3.16 (3H, a), 3.23 (3H, s), 5.62 (1H, d, J= 12.2 Hz), 7.24-7.29 (1H, m), 7.39 (1H, t, J= 7.6 Hz), 7.5 (1H, m), 7.55-7.62 (1H, m), 7.69-7.86 (5H, m)

N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-N-methyl-4-cyanobenzenesulfonamide

^1H NMR (400 MHz, $CDCl_3$): δ 2.94 (3H, a), 3.17 (3H, a), 3.22 (3H, s), 5.6 (1H, d, J= 12.2 Hz), 7.24-7.3 (1H, m), 7.39 (1H, t, J= 7.9 Hz), 7.51 (1H, m), 7.64-7.7 (2H, m), 7.73-7.82 (4H, m)

N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-N-methyl-3-nitrobenzenesulfonamide

^1H NMR (400 MHz, $CDCl_3$): δ 2.93 (3H, a), 3.16 (3H, a), 3.26 (3H, s), 5.6 (1H, d, J= 12.2 Hz), 7.27-7.32 (2H, m), 7.39 (1H, t, J= 7.9 Hz), 7.48 (1H, m), 7.62-7.82 (4H, m), 8.4-8.44 (1H, m)

N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-N-methyl-4-nitrobenzenesulfonamide

^1H NMR (400 MHz, $CDCl_3$): δ 2.92 (3H, a), 3.17 (3H, a), 3.25 (3H, s), 5.6 (1H, d, J= 12.5 Hz), 7.25-7.29 (1H, m), 7.39 (1H, t, J= 7.9 Hz), 7.53 (1H, m), 7.73 (2H, d, J= 9 Hz), 8.4-8.44 (1H, m), 7.77-7.84 (2H, m), 8.3 (2H, d, J= 9 Hz)

N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-N-methyl-2-thiophenesulfonamide

^1H NMR (400 MHz, $CDCl_3$): δ 2.85 (3H, a), 3.07 (3H, a), 3.19 (3H, s), 5.54 (1H, d, J= 12.5 Hz), 6.99 (1H, dd, J= 4.8 Hz), 7.19-7.32 (3H, m), 7.48-7.53 (2H, m), 7.67-7.74 (2H, m)

N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-N-methyl-5-methyl-4-isoxazolesulfonamide

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.13 (3H, s), 2.88 (3H, a), 3.11 (3H, s), 3.19 (3H, m), 5.53 (1H, d, J= 12.5 Hz), 7.21-7.28 (1H, m), 7.35 (1H, t, J= 7.9 Hz), 7.56-7.81 (3H, m), 8.15 (1H, m)

N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-N-methyl-2-trifluoromethyl-5-methyl-3-furansulfonamide

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.13 (3H, s), 2.94 (3H, a), 3.27 (3H, s), 5.61 (1H, d, J= 12.2 Hz), 6.8 (1H, m), 7.3-7.44 (2H, m), 7.66 (1H, t), 7.79-7.86 (2H, m)

N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-N-methyl-6-(morpholin-4-yl)-3-pyridinesulfonamide

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.88 (3H, a), 3.13 (3H, s), 3.54-3.58 (4H, m), 3.71-3.75 (4H, m), 5.59 (1H, d, J= 12.5 Hz), 6.43 (1H, dd, J= 9.1 Hz), 7.21-7.3 (2H, m), 7.35 (1H, dd, J= 9.1 Hz), 7.58-7.6 (1H, m), 7.69-7.74 (2H, m), 8.3 (1H, dd, J= 2.6 y 0.8 Hz)

N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-N-methyl-2,4-dimethyl-5-thiazolesulfonamide

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.06 (3H, s), 2.6 (3H, s), 2.88 (3H, a), 3.1 (3H, a), 3.23 (3H, s), 5.56 (1H, dd, J= 12.2 Hz), 7.23-7.38 (2H, m), 7.7-7.8 (3H, m)

N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-N-methyl-cyclopropanesulfonamide

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.03-1.12 (1H, m), 1.23-1.32 (1H, m), 1.5-1.54 (1H, m), 2.26-2.37 (1H, m), 2.88 (3H, a),

3.09 (3H, a), 3.16-3.28 (1H, m), 3.31 (3H, s), 5.62 (1H, d, J= 12.2 Hz), 7.3-7.37 (1H, m), 7.44-7.48 (1H, m), 7.7-7.77 (2H, m), 7.87-7.88 (1H, m)

N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-N-methyl-benzylsulfonamide

^1H NMR (400 MHz, $CDCl_3$): δ 3.05 (3H, a), 3.25 (6H, s), 4.37 (2H, s), 5.76 (1H, d, J= 12.2 Hz), 7.44-7.51 (7H, m), 7.83-7.93 (3H, m)

N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-N-methyl-vinylsulfonamide

^1H NMR (400 MHz, $CDCl_3$): δ 2.92 (3H, a), 3.14 (3H, a), 5.66 (1H, d, J= 12.2 Hz), 5.97 (1H, dd), 6.13 (1H, dd), 6.39 (1H, dd), 7.31-7.47 (2H, m), 7.7-7.75 (2H, m), 7.87 (1H, d, J= 12.2 Hz)

N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-N-methyl 3,5-dimethyl-4-isoxazolesulfonamide

^1H NMR (400 MHz, $CDCl_3$): δ 2.03 (3H, s), 2.27 (3H, s), 2.94 (3H, a), 3.16 (3H, a), 3.27 (3H, s), 5.58 (1H, d, J= 12.2 Hz), 7.31-7.43 (2H, m), 7.66 (1H, m), 7.77-7.85 (2H, m)

N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-N-methyl 1,3,5-trimethyl-4-pyrazolesulfonamide

^1H NMR (400 MHz, $CDCl_3$): δ 1.96 (3H, s), 2.84 (3H, a), 3.16 (3H, a), 3.2 (3H, a), 3.68 (3H, s), 5.63 (1H, d, J= 12.5 Hz), 7.34-7.37 (2H, m), 7.63 (1H, m), 7.76-7.82 (2H, m)

Example 16: General procedure for the preparation of pyrazolo[1,5-a]pyrimidines of general formula (I) following Scheme 1

N-prop-2-inyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a] pyrimidin-7-yl]-phenyl}-methanesulfonamide

0.1 g (0.33 mmol) of 4-thiophene-2-carbonyl-2H-pyrazol-3-ylamine and 0.063 g (0.33 mmol) of N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-N-prop-2-inyl-methanesulfonamide were dissolved in 10 ml of glacial acetic acid. After refluxing for 8 hours, the solvent was removed by reduced pressure distillation. To the resultant residue 10 ml of dichloromethane and 10 ml of a saturated solution of sodium bicarbonate were added. The two layers were separated, and the aqueous layer was washed with 10 ml of dichloromethane. The organic layers were washed with 10 ml of water and dried over magnesium sulfate. The dichloromethane layer was evaporate to dryness to yield an oil which, in the presence of ethyl acetate gave a yellow solid, 111 mg (yield= 78%) N-prop-2-inyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-methanesulfonamide.

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.54 (1H, s), 3.12 (3H, s), 4.54 (2H, s), 7.15 (1H, d, J= 4 Hz), 7.19-7.21 (1H, m), 7.65 (1H, t, J= 7.6 Hz), 7.69-7.71 (1H, m), 7.84-7.87 (1H, m), 8.03-8.06 (1H, m), 8.08-8.10 (1H, m).8.31 (1H, t, J= 2 Hz).8.71 (1H, s).8.82 (1H, d, J= 4.4 Hz)

MS (ES) m/z = 437 (MH+)

HPLC = 100%

As described in the general procedure of Example 16, the following exemplified compounds were prepared:

Example 17: N-propyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-ethanesulfonamide

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.94 (3H, t, J= 7.6 Hz), 1.42 (3H, t, J= 7.6 Hz), 1.54-1.63 (2H, m), 3.08-3.31 (2H, m), 3.75 (2H, t, J= 7.2 Hz), 7.16 (1H, d, J= 4.4 Hz), 7.19-7.21 (1H, m), 7.59-7.65 (2H, m), 7.69-7.71 (1H, m), 7.99-8.02 (1H, m).8.09-8.11 (2H, m, J= 2 Hz).8.71 (1H, s).8.82 (1H, d, J= 4.4 Hz)
MS (ES) m/z = 455 (MH+)
HPLC = 97.86%

Example 18: N-ethyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-ethanesulfonamide

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.22 (3H, t, J= 6.8 Hz), 1.43 (3H, t, J= 7.6 Hz), 3.11 (2H, c, J= 7.6 Hz), 3.85 (2H, c, J= 6.8 Hz), 7.16 (1H, d, J= 4.4 Hz), 7.19-7.21 (1H, m, J= 4.4 Hz), 7.58-7.66 (2H, m), 7.69-7.71 (1H, m), 7.99-8.02 (1H, m), 8.09-8.11 (2H, m).8.71 (1H, s).8.82 (1H, d, J= 4.4 Hz)
MS (ES) m/z = 441 (MH+)
HPLC = 97.73%

Example 19: N-prop-2-inyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-2-propanesulfonamide

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.44 (6H, d, J= 6.4 Hz), 2.42 (1H, m), 3.44-3.51 (1H, m), 4.56 (1H, s), 7.15 (1H, d, J= 4

Hz), 7.19-7.20 (1H, m), 7.65 (1H, t, J= 8 Hz), 7.69-7.71 (1H, m), 7.76-7.79 (1H, m), 8.02-8.05 (1H, m).8.09-8.11 (1H, m).8.24-8.25 (1H, m).8.7 (1H, s).8.82 (1H, d, J= 4.4 Hz)

MS (ES) m/z = 465 (MH+)

HPLC = 100%

Example 20: N-methyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-ethanesulfonamide

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.41 (3H, t, J= 7.2 Hz), 3.12 (2H, c, J= 7.6 Hz), 3.45 (3H, s), 7.15 (1H, d, J= 4.4 Hz), 7.19-7.23 (1H, m, J= 4.4 Hz), 7.61-7.63 (2H, m), 7.69-7.71 (1H, m), 7.92-7.95 (1H, m), 8.09-8.11 (1H, m), 8.13-8.14 (1H, m).8.71 (1H, s).8.82 (1H, d, J= 4.4 Hz)

MS (ES) m/z = 427 (MH+)

HPLC = 84.2%

Example 21: N-butyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-ethanesulfonamide

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.91 (3H, t, J= 7.2 Hz), 1.36-1.44 (5H, m), 1.52-1.57 (2H, m), 3.1 (2H, c, J= 7.6 Hz), 3.78 (2H, t, J= 7.2 Hz), 7.16 (1H, d, J= 4.4 Hz), 7.20-7.25 (1H, m), 7.61-7.63 (2H, m), 7.69-7.71 (1H, m), 7.99-8.02 (1H, m).8.09-8.11 (2H, m).8.71 (1H, s).8.82 (1H, d, J= 4.4 Hz)

MS (ES) m/z = 469 (MH+)

HPLC = 99.06%

Example 22: 7-(3-(2-isothiazolidinyl-1,1-dioxide)-phenyl)-3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]pyrimidine

^1H NMR (400 MHz, $CDCl_3$): δ 2.57-2.61 (2H, m), 3.43 (2H, t, J= 7.6 Hz), 3.87 (2H, t, J= 6.4 Hz), 7.14 (1H, d, J= 4 Hz), 7.19 (1H, t), 7.46-7.50 (1H, m), 7.58 (1H, t), 7.68-7.69 (1H, d, J= 4 Hz), 7.78-7.79 (1H, d), 7.9 (1H, s).8.09 (1H, d, J= 3.2 Hz).8.69 (1H, s).8.79 (1H, d, J= 4.4 Hz)

MS (ES) m/z = 425 (MH+)

HPLC = 97.1%

Example 23: N-methyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-2-propane-sulfonamide

^1H NMR (400 MHz, $CDCl_3$): δ 1.4 (6H, d, J= 6.8 Hz), 3.36-3.41 (1H, m), 3.47 (3H, s), 7.15 (1H, d, J= 4.4 Hz), 7.18-7.21 (1H, m), 7.58-7.64 (2H, m), 7.69-7.71 (1H, m), 7.89-7.93 (1H, m), 8.09-8.10 (1H, m), 8.14-8.16 (1H, m).8.7 (1H, s).8.81 (1H, d, J= 4.4 Hz)

MS (ES) m/z = 441 (MH+)

HPLC = 96.35%

Example 24: N-ethyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-2-propane-sulfonamide

^1H NMR (400 MHz, $CDCl_3$): δ 1.21 (3H, t, J= 6.8 Hz), 1.41 (6H, d, J= 6.4 Hz), 3.28-3.32 (1H, m), 3.87 (2H, c, J= 7.2 Hz), 7.16 (1H, d, J= 4.4 Hz), 7.18-7.21 (1H, m), 7.61-7.62 (2H, m), 7.69-7.71 (1H, m), 7.9-8.1 (1H, m), 8.09-8.12 (1H, m).8.7 (1H, s).8.81 (1H, d, J= 4.4 Hz).

MS (ES) m/z = 455 (MH+)

HPLC = 88.35%

Example 25: N-propyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-2-propane-sulfonamide

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.93 (3H, t, J= 7.2 Hz), 1.41 (6H, d, J= 6.8 Hz), 1.57 (2H, q, J= 7.2 Hz), 3.3 (1H, m, J= 6.8 Hz), 3.77 (2H, t, J= 7.2 Hz), 7.16 (1H, d, J= 4.4 Hz), 7.19-7.21 (1H, m), 7.61-7.63 (2H, m), 7.69-7.71 (1H, m), 7.99-8.11 (1H, m), 8.09-8.13 (2H, m), 8.7 (1H, s), 8.81 (1H, d, J= 4.4 Hz)
MS (ES) m/z = 469 (MH+)
HPLC = 97%

Example 26: N-butyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-2-propane-sulfonamide

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.9 (3H, t, J= 7.2 Hz), 1.36 (2H, q, J= 8 Hz), 1.41 (6H, d, J= 6.8 Hz), 1.51-1.55 (2H, m), 3.29 (1H, m, J= 6.4 Hz), 8.81 (2H, t, J= 6.8 Hz), 7.16 (1H, d, J= 4.4 Hz), 7.19-7.21 (1H, m), 7.62-7.63 (2H, m), 7.70-7.71 (1H, m), 7.99-8.01 (1H, m), 8.10-8.14 (2H, m), 8.7 (1H, s), 8.82 (1H, d, J= 4.4 Hz)
MS (ES) m/z = 483 (MH+)
HPLC = 100%

Example 27: N-[3-(3-cyano-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-N-prop-2-inyl-methanesulfonamide

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.53 (1, s), 3.1 (3H, s), 4.53 (2H, s), 7.19 (1H, d, J= 4.4 Hz), 7.65 (1H, t, J= 7.6 Hz), 7.85-7.88 (1H, m, J= 4.4 Hz), 8.0-8.29 (1H, m), 8.27-8.28 (1H, m), 8.42 (1H, s), 8.79 (1H, d, J= 4.4 Hz)

MS (ES) m/z = 352 (MH+)
HPLC = 95.78%

Example 28: N-[3-(3-cyano-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-N-propyl-ethanesulfonamide

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.93 (3H, t, J= 7.6 Hz), 1.41 (3H, t, J= 7.2 Hz), 1.54-1.59 (2H, m), 3.01 (2H, q, J= 7.2 Hz), 3.74 (2H, t, J= 7.2 Hz), 7.2 (1H, d, J= 4.4 Hz), 7.59-7.65 (2H, m), 7.96-7.99 (1H, m), 8.07-8.08 (1H, m), 8.41 (1H, s), 8.78 (1H, d, J= 4.4 Hz)
MS (ES) m/z = 370 (MH+)
HPLC = 98%

Example 29: N-[3-(3-cyano-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-N-ethyl-ethanesulfonamide

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.21 (3H, t, J= 7.2 Hz), 1.42 (3H, t, J= 7.6 Hz), 3.09 (2H, q, J= 7.6 Hz), 3.84 (2H, q, J= 7.2 Hz), 7.2 (1H, d, J= 4 Hz), 7.58-7.65 (2H, m), 7.97-7.99 (1H, m), 8.07 (1H, t, J= 1.6 Hz), 8.42 (1H, s), 8.78 (1H, d, J= 4.8 Hz)
MS (ES) m/z = 356 (MH+)
HPLC = 99%

Example 30: N-[3-(3-cyano-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-N-prop-2-inyl-propane-2-sulfonamide

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.43 (6H, d, J= 7.2 Hz), 2.41-2.42 (1H, m), 3.43-3.50 (1H, m), 3.54 (2H, s), 7.2 (1H, d, J= 4 Hz), 7.63 (1H, t, J= 7.6 Hz), 7.77-7.80 (1H, m), 7.99-8.02 (1H, m), 8.21-8.22 (1H, m), 8.42 (1H, s).8.78 (1H, d, J= 4.4 Hz)

MS (ES) m/z = 380 (MH+)
HPLC = 97.46%

Example 31: N-[3-(3-cyano-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-N-methyl-ethanesulfonamide

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.4 (3H, t, J= 7.2 Hz), 3.11 (2H, q, J= 7.2 Hz), 3.43 (3H, s), 7.19 (1H, d, J= 4.4 Hz), 7.60-7.63 (2H, m), 7.89-7.92 (1H, m), 8.11 (1H, a), 8.42 (1H, s), 8.78 (1H, d, J= 4.4 Hz)
MS (ES) m/z = 342 (MH+)
HPLC = 91%

Example 32: N-[3-(3-cyano-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-N-butyl-ethanesulfonamide

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.43 (3H, t, J= 7.2 Hz), 2.49 (1H, t, J= 2.4 Hz), 3.26 (2H, q, J= 7.2 Hz), 4.54 (2H, d, J= 2.4 Hz), 7.2 (1H, d, J= 4 Hz), 7.64 (1H, t, J= 8 Hz), 7.82-7.85 (1H, m), 8.00-8.03 (1H, m), 8.25 (1H, t, J= 2 Hz), 8.42 (1H, s), 8.79 (1H, d, J= 4.4 Hz)
MS (ES) m/z = 366 (MH+)
HPLC = 98%

Example 33: 7-(3-(2-isothiazolidinyl-1,1-dioxide)-phenyl)-3-cyano-pyrazolo[1,5-a]pyrimidine

^{1}H NMR (400 MHz, DMSO-d_6): δ 2.47-2.51 (2H, m), 3.61 (2H, t, J= 7.6 Hz), 3.87 (2H, t, J= 6.8 Hz), 7.52-7.56 (1H, m), 7.6 (1H, d, J= 4.8 Hz), 7.66 (1H, t), 7.8-7.85 (2H, m), 8.88 (1H, s), 8.95 (1H, d, J= 4.4 Hz)
MS (ES) m/z = 340 (MH+)
HPLC = 91.47%

Example 34: N-[3-(3-cyano-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-N-methyl-2-propanesulfonamide

^1H NMR (400 MHz, $CDCl_3$): δ 1.39 (6H, d, J= 6.8 Hz), 3.38 (1H, m), 3.45 (3H, s), 7.19 (1H, d, J= 4 Hz), 7.56-7.66 (2H, m), 7.87-7.90 (1H, m), 8.125 (1H, t, J= 2 Hz), 8.41 (1H, s), 8.78 (1H, d, J= 4 Hz)
MS (ES) m/z = 356 (MH+)
HPLC = 91%

Example 35: N-[3-(3-cyano-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-N-ethyl-2-propanesulfonamide

^1H NMR (400 MHz, $CDCl_3$): δ 1.95 (3H, t, J= 7.2 Hz), 1.41 (6H, d, J= 6.8 Hz), 3.28 (1H, m), 3.86 (2H, q, J= 7.2 Hz), 7.2 (1H, d, J= 4.4 Hz), 7.61-7.62 (2H, m), 7.96-7.99 (1H, m), 8.08-8.09 (1H, m), 8.41 (1H, s), 8.78 (1H, d, J= 4 Hz)
MS (ES) m/z = 370 (MH+)
HPLC = 98%

Example 36: N-[3-(3-cyano-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-N-butyl-2-propanesulfonamide

^1H NMR (400 MHz, $CDCl_3$): δ 0.89 (3H, t, J= 7.2 Hz), 1.32-1.36 (2H, m), 1.53-1.56 (6H, d, J= 6.8 Hz), 1.49-1.51 (2H, m), 3.27 (1H, m), 3.79 (2H, t, J= 7.6 Hz), 7.2 (1H, d, J= 4.4 Hz), 7.61-7.63 (2H, m), 7.95-7.98 (1H, m), 8.1 (1H, a), 8.41 (1H, s), 8.78 (1H, d, J= 4 Hz)
MS (ES) m/z = 398 (MH+)
HPLC = 95%

Example 37: N-[3-(3-cyano-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-N-propyl-2-propanesulfonamide

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.92 (3H, t, J= 7.2 Hz), 1.4 (6H, d, J= 6.8 Hz), 1.53-1.56 (2H, m), 3.27 (1H, m), 3.76 (2H, t, J= 7.6 Hz), 7.2 (1H, d, J= 4.4 Hz), 7.61-7.63 (2H, m), 7.96-7.98 (1H, m), 8.1 (1H, a), 8.41 (1H, s), 8.78 (1H, d, J= 4 Hz)
MS (ES) m/z = 384 (MH+)
HPLC = 98.05%

Example 38: N-[3-(3-cyano-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-N-prop-2-inyl-ethanesulfonamide

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.2 (3H, t, J= 7.6 Hz), 2.48 (1H, s), 3.25 (2H, c, J= 7.2 Hz), 4.54 (2H, s), 7.2 (1H, d, J= 4 Hz), 7.64 (1H, t, J= 8.4 Hz), 7.82-7.85 (1H, m), 7.99-8.03 (1H, m), 8.26-8.26 (1H, m), 8.42 (1H, s).8.79 (1H, d, J= 4.1 Hz)
MS (ES) m/z = 366 (MH+)
HPLC = 97.7%

Example 39: N-methyl-N-{3-[3-(pyridin-2-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-methanesulfonamide

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.92 (3H, s), 3.41 (3H, s), 7.17 (1H, d, J= 4.4 Hz), 7.48-7.51 (1H, m), 7.62-7.63 (2H, m), 7.90-7.94 (2H, m), 8.16-8.16 (1H, m), 8.24 (1H, d, J= 6.8 Hz), 8.73-8.75 (1H, m), 8.90 (1H, d, J= 4.4 Hz), 9.36 (1H, s)
MS (ES) m/z = 408 (MH+)
HPLC = 99%

Example 40: N-ethyl-N-{3-[3-(pyridin-2-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-methanesulfonamide

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.22 (3H, t, J= 7.2 Hz), 2.97 (3H, s), 3.82 (2H, q, J= 7.2 Hz), 7.18 (1H, d, J= 4 Hz), 7.48-7.51 (1H, m), 7.59-7.67 (2H, m), 7.90-7.94 (1H, m), 7.98-8.00 (1H, m), 8.15 (1H, s), 8.24 (1H, d, J= 7.6 Hz), 8.75 (1H, d, J= 4.8 Hz), 8.9 (1H, d, J= 4.4 Hz), 9.36 (1H, s)
MS (ES) m/z = 422 (MH+)
HPLC = 100%

Example 41: N-prop-2-inyl-N-{3-[3-(pyridin-2-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-methanesulfonamide

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.52-2.53 (1H, m), 3.12 (3H, s), 4.53-4.54 (2H, m), 7.17 (1H, d, J= 4.4 Hz), 7.48-7.52 (1H, m), 7.65 (2H, t, J= 8 Hz), 7.82-7.85 (1H, m), 7.92 (1H, t, J= 0.8 Hz), 8.03-8.06 (1H, m), 8.24 (1H, d, J= 8.4 Hz), 8.35 (1H, s), 8.75 (1H, d, J= 5.6 Hz), 8.9 (1H, d, J= 5.6 Hz), 9.37 (1H, s)
MS (ES) m/z = 432 (MH+)
HPLC = 96%

Example 42: N-methyl-N-{3-[3-(pyridin-2-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-ethanesulfonamide

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.4 (3H, t, J= 7.6 Hz), 3.12 (2H, q, J= 7.6 Hz), 3.44 (3H, s), 7.17 (1H, d, J= 4.4 Hz), 7.48-7.51 (1H, m), 7.61-7.64 (2H, m), 7.88-7.93 (2H, m), 8.16 (1H, t, J= 2 Hz), 8.24 (1H, d, J= 8.4 Hz), 8.74-8.75 (1H, m), 8.89 (1H, d, J= 5.2 Hz), 9.36 (1H, s)
MS (ES) m/z = 422 (MH+)

HPLC = 100%

Example 43: N-ethyl-N-{3-[3-(pyridin-2-carbonyl)-pyrazolo [1,5-a]pyrimidin-7-yl]-phenyl}-ethanesulfonamide

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.35 (3H, t, J= 7.2 Hz), 1.33 (3H, t, J= 7.2 Hz), 3.05 (2H, q, J= 7.2 Hz), 3.77 (2H, q, J= 7.2 Hz), 7.14 (1H, d, J= 4.8 Hz), 7.40-7.43 (1H, m), 7.54-7.56 (2H, m), 7.82-7.85 (1H, m), 7.92-7.93 (1H, m), 8.1 (1H, s), 8.13 (1H, d, J= 8 Hz), 8.66 (1H, d, J= 4.4 Hz), 8.81 (1H, d, J= 4.4 Hz), 9.28 (1H, s)
MS (ES) m/z = 436 (MH+)
HPLC = 95%

Example 44: N-prop-2-inyl-N-{3-[3-(pyridin-2-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-ethanesulfonamide

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.42 (3H, t, J= 7.2 Hz), 2.47 (1H,), 3.26 (2H, q, J= 7.2 Hz), 4.54 (2H, d, J= 2.4 Hz), 7.17 (1H, d, J= 4.8 Hz), 7.48-7.51 (1H, m), 7.63 (1H, t, J= 7.6 Hz, 7.8-7.82 (1H, m), 7.89-7.93 (1H, m), 8.02-8.05 (1H, m), 8.23 (1H, d, J= 8 Hz), 8.3 (1H, t, J= 2 Hz), 8.73-8.75 (1H, m), 8.89 (1H, d, J= 5.2 Hz), 9.36 (1H, s)
MS (ES) m/z = 446 (MH+)
HPLC = 98%

Example 45: N-methyl-N-{3-[3-(pyridin-4-carbonyl)-pyrazolo [1,5-a]pyrimidin-7-yl]-phenyl}-methanesulfonamide

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.92 (3H, s), 3.41 (3H, s), 7.2 (1H, d, J= 4.4 Hz), 7.26-7.64 (2H, m), 7.71-7.73 (2H, m), 7.93-7.96 (1H, m), 8.127-8.129 (1H, m), 8.57 (1H, s), 8.81-8.83 (3H, m)

MS (ES) m/z = 408 (MH+)
HPLC = 95%

Example 46: N-ethyl-N-{3-[3-(pyridin-4-carbonyl)-pyrazolo [1,5-a]pyrimidin-7-yl]-phenyl}-methanesulfonamide

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.22 (3H, t, J= 7.2 Hz), 2.96 (3H, s), 3.82 (2H, q, J= 7.2 Hz), 7.22 (1H, d, J= 4.4 Hz), (1H, m), 5.73 (2H, d, J= 5.6 Hz), 8.01 (1H, d, J= 7.6 Hz), 8.1 (1H, t, J= 2 Hz), 8.57 (1H, s), 8.82-8.84 (3H, m)
MS (ES) m/z = 422 (MH+)
HPLC = 89%

Example 47: N-methyl-N-{3-[3-(pyridin-4-carbonyl)-pyrazolo [1,5-a]pyrimidin-7-yl]-phenyl}-ethanesulfonamide

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.39 (3H, t, J= 7.2 Hz), 3.11 (2H, q, J= 7.2 Hz), 3.44 (3H, s), 7.2 (1H, d, J= 4.8 Hz), 7.62-7.63 (2H, m), 7.71-7.72 (2H, m), 7.92-7.94 (1H, m), 8.13-8.14 (1H, m), 8.57 (1H, s), 8.81-8.83 (3H, m)
MS (ES) m/z = 422 (MH+)
HPLC = 94%

Example 48: N-ethyl-N-{3-[3-(pyridin-4-carbonyl)-pyrazolo [1,5-a]pyrimidin-7-yl]-phenyl}-ethanesulfonamide

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.13 (3H, t, J= 7.2 Hz), 1.318 (3H, t, J= 7.2 Hz), 3.04 (2H, q, J= 7.2 Hz), 3.77 (2H, q, J= 7.2 Hz), 7.18 (1H, d, J= 4.8 Hz), 7.52-7.58 (2H, m), 7.61-7.94 (2H, m), 8.05 (1H, s), 8.47 (1H, s), 8.71-8.73 (3H, m)
MS (ES) m/z = 436 (MH+)
HPLC = 89%

Example 49: N-prop-2-inyl-N-{3-[3-(pyridin-4-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-ethanesulfonamide

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.22 (3H, t, J= 7.2 Hz), 2.96 (3H, s), 3.82 (2H, q, J= 7.2 Hz), 7.22 (1H, d, J= 4.4 Hz), 7.58-7.60 (1H, m), 7.66 (1H, t, J= 8 Hz), 7.71-7.73 (2H, m), 8.01 (1H, d, J= 7.6 Hz), 8.1 (1H, t, J= 2 Hz), 8.57 (1H, s), 8.82-8.84 (3H, m)
MS (ES) m/z = 422 (MH+)
HPLC = 89%

Example 50: N-prop-2-inyl-N-{3-[3-(pyridin-4-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-methanesulfonamide

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.53 (1H, t, J= 2 Hz), 3.11 (3H, s), 4.54 (2H, d, J= 2.4 Hz), 7.2 (1H, d, J= 4.4 Hz), 7.66 (1H, t, J= 7.6 Hz), 7.72-7.73 (2H, m), 7.86-7.89 (1H, m), 8.03-8.05 (1H , m), 8.31 (1H, t, J= 2 Hz), 8.56 (1H, s), 8.82-8.84 (3H, m)
MS (ES) m/z = 432 (MH+)
HPLC = 93%

Example 51: N-methyl-N-{3-[3-(fluorobenzene-4-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-methanesulfonamide

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.93 (3H, s), 3.42 (3H, s), 7.15-7.20 (3H, m), 7.61-7.63 (2H, m), 7.94-7.99 (3H, m), 8.12-8.13 (1H, m), 8.55 (1H, s), 8.78 (1H, d, J= 4.4 Hz)
MS (ES) m/z = 425 (MH+)
HPLC = 98%

Example 52: N-ethyl-N-{3-[3-(fluorobenzene-4-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-methanesulfonamide

^1H NMR (400 MHz, $CDCl_3$): δ 1.23 (3H, t, J= 7.2 Hz), 2.97 (3H, s), 3.82 (2H, q, J= 7.2 Hz), 7.16-7.20 (3H, m), 7.56-7.60 (1H, m), 7.65 (1H, t, J= 8 Hz), 7.96-8.02 (3H, m), 8.1 (1H, t, J= 2 Hz), 8.55 (1H, s), 8.79 (1H, d, J= 4.4 Hz)
MS (ES) m/z = 439 (MH+)
HPLC = 98%

Example 53: N-methyl-N-{3-[3-(fluorobenzene-4-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-ethanesulfonamide

^1H NMR (400 MHz, $CDCl_3$): δ 1.38 (3H, t, J= 7.2 Hz), 3.11 (2H, q, J= 7.2 Hz), 3.42 (3H, s), 7.13-7.17 (3H, m), 7.59-7.61 (2H, m), 7.90-7.97 (3H, m, J= 8 Hz), 8.13 (1H, a), 8.53 (1H, s), 8.76 (1H, d, J= 4.4 Hz)
MS (ES) m/z = 439 (MH+)
HPLC = 94%

Example 54: N-ethyl-N-{3-[3-(fluorobenzene-4-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-ethanesulfonamide

^1H NMR (400 MHz, $CDCl_3$): δ 1.21 (3H, t, J= 7.2 Hz), 1.41 (3H, t, J= 7.2 Hz), 3.1 (2H, q, J= 7.2 Hz), 3.84 (2H, q, J= 7.2 Hz), 7.14-7.18 (3H, m), 7.58 (2H, m), 7.94-8.01 (3H, m), 8.1 (1H, a), 8.54 (1H, s), 8.77 (1H, d, J= 4.4 Hz)
MS (ES) m/z = 453 (MH+)
HPLC = 99%

Example 55: N-prop-2-inyl-N-{3-[3-(fluorobenzene-4-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-ethanesulfonamide

^1H NMR (400 MHz, $CDCl_3$): δ 1.43 (3H, t, J= 7.2 Hz), 2.48 (1H, t, J= 2.4 Hz), 3.27 (2H, q, J= 7.2 Hz), 4.54 (2H, d,

J= 2.4 Hz), 7.15-7.2 (3H, m), 7.64 (1H, t, J= 8 Hz), 7.81-7.84 (1H, m), 7.96-8.04 (3H, m), 8.28 (1H, a), 8.56 (1H, s), 8.79 (1H, d, J= 4.4 Hz)

MS (ES) m/z = 463 (MH+)

HPLC = 96%

Example 56: N-prop-2-inyl-N-{3-[3-(fluorobenzene-4-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-methanesulfonamide

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.54 (1H, t, J= 2 Hz), 3.1 (3H, s), 4.52 (2H, d, J= 2 Hz), 7.14-7.18 (3H, m), 7.64 (1H, t, J= 7.6 Hz), 7.83-7.86 (1H, m), 7.94-7.96 (2H, m), 8.02-8.04 (1H, m), 8.3 (1H, t, J= 2 Hz), 8.54 (1H, s), 8.77 (1H, d, J= 4 Hz)

MS (ES) m/z = 449 (MH+)

HPLC = 96%

Example 57: N-methyl-N-{3-[3-(4-methoxybenzoyl)-pyrazolo [1,5-a]pyrimidin-7-yl]-phenyl}-methanesulfonamide

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.93 (3H, s), 3.42 (3H, s), 3.9 (3H, s), 6.97-7.01 (2H, m), 7.12 (1H, d, J= 4.4 Hz), 7.61-7.65 (2H, m), 7.94-7.99 (3H, m), 8.13 (1H, a), 8.55 (1H, s), 8.78 (1H, d, J= 3.6 Hz)

MS (ES) m/z = 437 (MH+)

HPLC = 99%

Example 58: N-ethyl-N-{3-[3-(4-methoxybenzoyl)-pyrazolo [1,5-a]pyrimidin-7-yl]-phenyl}-methanesulfonamide

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.23 (3H, t, J= 7.2 Hz), 2.97 (3H, s), 3.82 (2H, q, J= 7.2 Hz), 3.9 (3H, s), 6.98-7.00

(2H, m), 7.14 (1H, d, J= 4 Hz), 7.59-7.60 (1H, m), 7.65 (1H, t, J= 8 Hz), 7.96-8.03 (3H, m), 8.1 (1H, t, J= 2 Hz).8.55 (1H, s), 8.78 (1H, d, J= 4 Hz)
MS (ES) m/z = 451 (MH+)
HPLC = 98%

Example 59: N-methyl-N-{3-[3-(4-methoxybenzoyl)-pyrazolo [1,5-a]pyrimidin-7-yl]-phenyl}-ethane-sulfonamide

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.41 (3H, t, J= 7.2 Hz), 3.13 (2H, q, J= 7.2 Hz), 3.45 (3H, s), 3.9 (3H, s), 6.98-7.00 (2H, m), 7.12 (1H, d, J= 4.4 Hz), 7.61-7.63 (2H, m), 7.93-7.98 (3H, m), 8.14 (1H, t, J= 1.2 Hz), 8.55 (1H, s), 8.78 (1H, d, J= 4 Hz)
MS (ES) m/z = 451 (MH+)
HPLC = 97%

Example 60: N-ethyl-N-{3-[3-(4-methoxybenzoyl)-pyrazolo [1,5-a]pyrimidin-7-yl]-phenyl}-ethanesulfonamide

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.23 (3H, t, J= 7.2 Hz), 1.43 (3H, t, J= 7.2 Hz), 3.12 (2H, q, J= 7.2 Hz), 3.86 (2H, q, J= 7.2 Hz), 3.91 (3H, s), 6.98-7.00 (2H, m), 7.14 (1H, d, J= 4 Hz), 7.6-7.65 (2H, m), 7.96-8.02 (3H, m), 8.11 (1H, t, J= 1.6 Hz), 8.55 (1H, s), 8.78 (1H, d, J= 4 Hz)
MS (ES) m/z = 465 (MH+)
HPLC = 98%

Example 61: N-prop-2-inyl-N-{3-[3-(4-methoxybenzoyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-ethanesulfonamide

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.43 (3H, t, J= 7.2 Hz), 2.48 (1H, t, J= 2.4 Hz), 3.27 (2H, q, J= 7.2 Hz), 3.9 (3H, s),

4.55 (2H, d, J= 2.4 Hz), 6.98-7.00 (2H, m), 7.13 (1H, d, J= 4.4 Hz), 7.64 (1H, t, J= 8 Hz), 7.80-7.83 (1H, m), 7.96-7.98 (2H, m).8.03-8.05 (1H, m), 8.28 (1H, a), 8.55 (1H, s), 8.78 (1H, d, J= 3.6 Hz)

MS (ES) m/z = 475 (MH+)

HPLC = 97%

Example 62: N-prop-2-inyl-N-{3-[3-(4-methoxybenzoyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-methanesulfonamide

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.53 (1H, t, J= 2 Hz), 3.11 (3H, s), 3.87 (3H, s), 4.53 (2H, d, J= 2 Hz), 6.98 (2H, d, J= 8.8 Hz), 7.12 (1H, d, J= 4.4 Hz), 7.63 (1H, t, J= 7.6 Hz), 7.82-7.84 (1H, m), 7.95 (2H, d, J= 8.8 Hz), 8.03 (1H, d, J= 7.6 Hz), 8.31 (1H, t, J= 2 Hz), 8.54 (1H, s), 8.76 (1H, d, J= 4.4 Hz)

MS (ES) m/z = 461 (MH+)

HPLC = 100%

Example 63: N-methyl-N-{3-[3-(4-methylbenzoyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-methanesulfonamide

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.5 (3H, s), 2.97 (3H, s), 3.46 (3H, s), 7.18 (1H, d, J= 4.4 Hz), 7.34 (2H, d, J= 8.4 Hz), 7.65-7.67 (2H, m), 7.89 (2H, d, J= 8 Hz), 7.98-8.00 (1H, m), 8.17 (1H, s), 8.58 (1H, s), 8.83 (1H, d, J= 4.4 Hz)

MS (ES) m/z = 421 (MH+)

HPLC = 99%

Example 64: N-ethyl-N-{3-[3-(4-methylbenzoyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-methanesulfonamide

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.23 (3H, t, J= 7.2 Hz), 2.45 (3H, s), 2.96 (3H, s), 3.82 (2H, q, J= 7.2 Hz), 7.15 (1H, d, J= 4.4 Hz), 7.29-7.3 (2H, m), 7.58-7.64 (2H, m), 7.83-7.85 (2H, m), 7.99-8.02 (1H, m), 8.1 (1H, t, J= 2 Hz), 8.53 (1H, s), 8.79 (1H, d, J= 4.8 Hz)
MS (ES) m/z = 435 (MH+)
HPLC = 96%

Example 65: N-methyl-N-{3-[3-(4-methylbenzoyl)-pyrazolo [1,5-a]pyrimidin-7-yl]-phenyl}-ethanesulfonamide

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.41 (3H, t, J= 7.2 Hz), 2.46 (3H, s), 3.12 (2H, q, J= 7.2 Hz), 3.44 (3H, s), 7.13 (1H, d, J= 4 Hz), 7.31 (2H, d, J= 8.4 Hz), 7.61-7.63 (2H, m), 7.85-7.87 (2H, m), 7.92-7.93 (1H, m), 8.13-8.14 (1H, m), 8.54 (1H, s), 8.79 (1H, d, J= 4.4 Hz)
MS (ES) m/z = 435 (MH+)
HPLC = 98%

Example 66: N-ethyl-N-{3-[3-(4-methylbenzoyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-ethanesulfonamide

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.22 (3H, t, J= 7.2 Hz), 1.42 (3H, t, J= 7.2 Hz), 2.46 (3H, s), 3.11 (2H, q, J= 7.2 Hz), 3.85 (2H, q, J= 7.2 Hz), 7.15 (1H, d, J= 4.4 Hz), 7.31 (2H, d, J= 8.2 Hz), 7.60-7.66 (2H, m), 7.84-7.86 (2H, m), 8 (1H, d, J= 7.6 Hz), 8.11 (1H, t, J= 1.6 Hz), 8.54 (1H, s), 8.8 (1H, d, J= 4.4 Hz)
MS (ES) m/z = 449 (MH+)
HPLC = 100%

Example 67: N-prop-2-inyl-N-{3-[3-(4-methylbenzoyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-ethanesulfonamide

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.43 (3H, t, J= 7.2 Hz), 2.46 (3H, s), 2.48 (1H, t, J= 2.4 Hz), 3.27 (2H, q, J= 7.2 Hz), 4.54 (2H, d, J= 2.4 Hz), 7.14 (1H, d, J= 4 Hz), 7.31 (2H, d, J= 8 Hz), 7.63 (1H, t, J= 8 Hz), 7.81-7.86 (3H, m), 8.03 (1H, d, J= 8 Hz), 8.28 (1H, t, J= 2 Hz), 8.54 (1H, s), 8.8 (1H, d, J= 4.4 Hz)

MS (ES) m/z = 459 (MH+)

HPLC = 98%

Example 68: N-prop-2-inyl-N-{3-[3-(4-methylbenzoyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-methanesulfonamide

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.46 (3H, s), 2.53 (1H, t, J= 2.4 Hz), 3.11 (3H, s), 4.54 (2H, d, J= 2.4 Hz), 7.14 (1H, d, J= 4 Hz), 7.3 (2H, d, J= 8 Hz), 7.64 (1H, t, J= 8 Hz), 7.83-7.86 (3H, m), 8.03-8.05 (1H, m), 8.31 (1H, t, J= 2 Hz), 8.54 (1H, s), 8.8 (1H, d, J= 4.4 Hz)

MS (ES) m/z = 445 (MH+)

HPLC = 98%

Example 69: N-methyl-N-{3-[3-(benzoyl)-pyrazolo[1,5-a] pyrimidin-7-yl]-phenyl}-methanesulfonamide

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.93 (3H, s), 3.42 (3H, s), 7.15 (1H, d, J= 4.4 Hz), 7.49-7.52 (2H, m), 7.58-7.63 (3H, m), 7.92-7.94 (3H, m), 8.13 (1H, a), 8.54 (1H, s), 8.81 (1H, d, J= 4.4 Hz)

MS (ES) m/z = 407 (MH+)

HPLC = 96%

Example 70: N-ethyl-N-{3-[3-(benzoyl)-pyrazolo[1,5-a] pyrimidin-7-yl]-phenyl}-methanesulfonamide

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.22 (3H, t, J= 7.2 Hz), 2.97 (3H, s), 3.82 (2H, q, J= 7.2 Hz), 7.17 (1H, d, J= 4.4 Hz), 7.49-7.52 (2H, m), 7.56-7.67 (3H, m), 7.91-7.94 (2H, m), 7.80-8.02 (1H, m), 8.11 (1H, t, J= 2 Hz), 8.53 (1H, s), 8.82 (1H, d, J= 4.4 Hz)
MS (ES) m/z = 421 (MH+)
HPLC = 98%

Example 71: N-methyl-N-{3-[3-(benzoyl)-pyrazolo[1,5-a] pyrimidin-7-yl]-phenyl}-ethanesulfonamide

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.39 (3H, t, J= 7.2 Hz), 3.11 (2H, q, J= 7.2 Hz), 3.43 (3H, s), 7.15 (1H, a), 7.47-7.61 (5H, m), 7.91 (3H, d, J= 7.6 Hz), 8.14 (1H, s), 8.52 (1H, s), 8.79 (1H, a)
MS (ES) m/z = 421 (MH+)
HPLC = 98%

Example 72: N-ethyl-N-{3-[3-(benzoyl)-pyrazolo[1,5-a] pyrimidin-7-yl]-phenyl}-ethanesulfonamide

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.23 (3H, t, J= 7.2 Hz), 1.42 (3H, t, J= 7.2 Hz), 1.56 (3H, s), 3.11 (2H, q, J= 7.2 Hz), 3.85 (2H, q, J= 7.2 Hz), 7.17 (1H, d, J= 4.4 Hz), 7.49-7.53 (2H, m), 7.58-7.66 (3H, m), 7.92-7.94 (2H, m), 8.01 (1H, d, J= 7.6 Hz), 8.11 (1H, t, J= 1.6 Hz), 8.54 (1H, s), 8.82 (1H, d, J= 4.8 Hz)
MS (ES) m/z = 435 (MH+)
HPLC = 100%

Example 73: N-prop-2-inyl-N-{3-[3-(benzoyl)-pyrazolo [1,5-a]pyrimidin-7-yl]-phenyl}-ethanesulfonamide
^{1}H NMR (400 MHz, $CDCl_3$): δ 1.43 (3H, t, J= 7.2 Hz), 2.48 (1H, t, J= 2.8 Hz), 3.27 (2H, q, J= 7.2 Hz), 4.54 (2H, d, J= 2.8 Hz), 7.16 (1H, d, J= 4.4 Hz), 7.49-7.52 (2H, m), 7.58-7.66 (2H, m), 7.82 (1H, d, J= 8 Hz), 7.93 (2H, d, J= 6.8 Hz), 8.04 (1H, d, J= 8 Hz), 8.29 (1H, a), 8.54 (1H, s), 8.81 (1H, d, J= 4.4 Hz)
MS (ES) m/z = 445 (MH+)
HPLC = 97%

Example 74: N-prop-2-inyl-N-{3-[3-(benzoyl)-pyrazolo [1,5-a]pyrimidin-7-yl]-phenyl}-methanesulfonamide

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.53 (1H, t, J= 2.4 Hz), 3.12 (3H, s), 4.54 (2H, d, J= 2.4 Hz), 7.16 (1H, d, J= 4.8 Hz), 7.49-7.53 (2H, m), 7.58-7.60 (1H, m), 7.65 (1H, t, J= 8 Hz), 7.84-7.86 (1H, m), 7.92-7.94 (2H, m), 8.04 (1H, d, J= 8 Hz), 8.32 (1H, t, J= 2 Hz), 8.54 (1H, s), 8.82 (1H, d, J= 4.4 Hz)
MS (ES) m/z = 431 (MH+)
HPLC = 97%

Example 75: N-methyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo [1,5-a]pyrimidin-7-yl]-phenyl}-2-phenylethene-sulfonamide

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.35 (3H, s), 6.78 (1H, d, J= 15.5 Hz), 7.13 (1H, d, J= 4.6 Hz), 7.21 (1H, dd), 7.48-7.52 (6H, m), 7.6-7.63 (2H, m), 7.71 (1H, dd), 7.92-7.96 (1H, m), 8.06 (1H, dd), 8.13 (1H, m).8.53 (1H, m).8.8 (1H, d, J= 4.6 Hz)
MS (ES) m/z = 501 (MH+)

HPLC = 96.98%

Example 76: N-methyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo [1,5-a]pyrimidin-7-yl]-phenyl}-2,2,2-trifluoroethane-sulfonamide

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.48 (3H, s), 3.87 (2H, c, J= 9.1 Hz), 7.16 (1H, d, J= 4.6 Hz), 7.21 (1H, dd), 7.65-7.67 (1H, m), 7.68 (1H, s), 7.72 (1H, dd), 7.98-8.02 (1H, m), 8.09 (1H, dd), 8.2 (1H, m).8.7 (1H, s).8.84 (1H, d, J= 4.6 Hz)
MS (ES) m/z = 481 (MH+)
HPLC = 99.05%

Example 77: N-methyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo [1,5-a]pyrimidin-7-yl]-phenyl}-2-chlorobenzene-sulfonamide

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.47 (3H, s), 7.06 (1H, d, J= 4.6 Hz), 7.19-7.23 (1H, m), 7.32-7.39 (1H, m), 7.46-7.57 (4H, m), 7.7-7.72 (1H, m), 7.92-8 (3H, m), 8.09-8.11 (1H, m), 8.67 (1H, s), 8.8 (1H, d, J= 4.6 Hz)
MS (ES) m/z = 510 (MH+)
HPLC = 99.81%

Example 78: N-methyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo [1,5-a]pyrimidin-7-yl]-phenyl}-3-chlorobenzenesulfonamide

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.27 (3H, s), 7.11 (1H, d, J= 4.6 Hz), 7.19-7.61 (7H, m), 7.7-7.72 (1H, m), 7.85 (1H, m), 7.97-8.01 (1H, m), 8.09-8.11 (1H, m), 8.68 (1H, s), 8.81 (1H, d, J= 4.6 Hz)

MS (ES) m/z = 510 (MH+)
HPLC = 97.44%

Example 79: N-methyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo [1,5-a]pyrimidin-7-yl]-phenyl}-4-chlorobenzenesulfonamide

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.25 (3H, s), 7.1 (1H, d, J= 4.6 Hz), 7.2-7.24 (1H, m), 7.33-7.37 (1H, m), 7.46-7.6 (5H, m), 7.72 (1H, dd), 7.85-7.87 (1H, m), 7.95-8 (1H, m), 8.09-8.11 (1H, m), 8.69 (1H, s).8.82 (1H, d, J= 4.6 Hz)
MS (ES) m/z = 510 (MH+)
HPLC = 99.69%

Example 80: N-methyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-2,4-dichlorobenzene-sulfonamide

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.46 (3H, s), 7.08 (1H, d, J= 4.6 Hz), 7.21 (1H, dd), 7.33 (1H, dd), 7.46-7.59 (3H, m), 7.71 (1H, dd), 7.87-7.98 (3H, m), 8.09 (1H, dd), 8.67 (1H, s), 8.81 (1H, d, J= 4.6 Hz)
MS (ES) m/z = 543 (MH+)
HPLC = 98.04%

Example 81: N-methyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-3,4-dichlorobenzene-sulfonamide

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.27 (3H, s), 7.11 (1H, d, J= 4.6 Hz), 7.21 (1H, dd), 7.37-7.47 (2H, m), 7.56-7.62 (2H, m), 7.7-7.72 (2H, m), 7.86-7.88 (1H, m), 7.94-7.99 (1H, m), 8.09 (1H, dd), 8.67 (1H, s).8.81 (1H, d, J= 4.6 Hz)

MS (ES) m/z = 543 (MH+)
HPLC = 98.03%

Example 82: N-methyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-2-cyanobenzene-sulfonamide

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.41 (3H, s), 7.15 (1H, d, J= 4.6 Hz), 7.2 (1H, dd), 7.34-7.39 (1H, m), 7.53-7.59 (1H, m), 7.69-7.77 (3H, m), 7.83-7.87 (1H, m), 7.91-8.01 (3H, m), 8.1 (1H, dd), 8.63 (1H, s).8.79 (1H, d, J= 4.6 Hz)
MS (ES) m/z = 500 (MH+)
HPLC = 99.32%

Example 83: N-methyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-3-cyanobenzene-sulfonamide

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.28 (3H, s), 7.13 (1H, d, J= 4.6 Hz), 7.19-7.22 (1H, m), 7.33-7.36 (1H, m), 7.56-7.72 (3H, m), 7.83-7.97 (5H, m), 8.09 (1H, d, J= 3.6 Hz), 8.66 (1H, s), 8.81 (1H, d, J= 4.6 Hz)
MS (ES) m/z = 500 (MH+)
HPLC = 96.69%

Example 84: N-methyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-4-cyanobenzene-sulfonamide

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.28 (3H, s), 7.12 (1H, d, J= 4.2 Hz), 7.2-7.32 (3H, m), 7.58 (1H, t, J= 8 Hz), 7.71-7.83 (4H, m), 7.91 (1H, a), 7.99 (1H, d, J= 7.6 Hz), 8.09 (1H, d, J= 3.3 Hz), 8.68 (1H, s), 8.83 (1H, d, J= 3.9 Hz)

MS (ES) m/z = 500 (MH+)
HPLC = 97.9%

Example 85: N-methyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-3-nitrobenzene-sulfonamide

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.3 (3H, s), 7.12 (1H, d, J= 4.6 Hz), 7.22 (1H, dd), 7.38-7.43 (1H, m), 7.6 (1H, t, J= 7.9 Hz), 7.7-7.77 (2H, m), 7.86-7.97 (3H, m), 8.09 (1H, dd), 8.4-8.5 (2H, m), 8.6 (1H, s).8.8 (1H, d, J= 4.6 Hz)
MS (ES) m/z = 520 (MH+)
HPLC = 99.14%

Example 86: N-methyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-4-nitrobenzene-sulfonamide

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.3 (3H, s), 7.13 (1H, d, J= 4.6 Hz), 7.23 (1H, dd, J= 4.8 - 0.9 Hz), 7.32-7.37 (1H, m), 7.6 (1H, t, J= 7.9 Hz), 7.73 (1H, dd, J= 4.8 - 3.6 Hz), 7.82 (2H, d, J= 9.1 Hz), 7.9 (1H, m), 7.95-7.99 (1H, m), 8.07 (1H, dd).8.36 (2H, d, J= 9.1 Hz).8.66 (1H, s).8.83 (1H, d, J= 4.6 Hz)
MS (ES) m/z = 520 (MH+)
HPLC = 96.18%

Example 87: N-methyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-2-thiophene-sulfonamide

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.35 (3H, s), 7.13-7.18 (2H, d), 7.23-7.31 (1H, m), 7.39-7.46 (2H, m), 7.58-7.68 (2H, m),

7.74-7.77 (1H, m), 7.93 (1H, d, J= 1.5 Hz), 8.06 (1H, dd, J= 7.9 - 1.2 Hz), 8.14 (1H, m), 8.72 (1H, s).8.85 (1H, d, J= 4.3 Hz)
MS (ES) m/z = 481 (MH+)
HPLC = 98.82%

Example 88: N-methyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-5-methyl-4-isoxazolylsulfonamide

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.3 (3H, s), 3.29 (3H, s), 7.11 (1H, d, J= 4.2 Hz), 7.21 (1H, dd, J= 5.2 - 3.9 Hz), 7.51-7.55 (1H, m), 7.63 (1H, t, J= 7.9 Hz), 7.71 (1H, dd, J= 5.2 - 1.2 Hz), 7.91-7.94 (2H, m), 8.07 (1H, dd), 8.32 (1H, d, J= 0.6 Hz).8.7 (1H, s).8.82 (1H, d, J= 4.2 Hz)
MS (ES) m/z = 480 (MH+)
HPLC = 96.78%

Example 89: N-methyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-2-trifluoromethyl-5-methyl-3-furylsulfonamide

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.23 (3H, s), 3.3 (3H, s), 7.11 (1H, d, J= 4.6 Hz), 7.2-7.24 (1H, m), 7.52-7.66 (2H, m), 7.72 (1H, dd, J= 4.9 - 1.2 Hz), 7.91-7.95 (2H, m), 8.07 (1H, dd), 8.67 (1H, s), 8.82 (1H, d, J= 4.2 Hz)
MS (ES) m/z = 547 (MH+)
HPLC = 98.88%

Example 90: N-methyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-6-(morpholin-4-yl)-3-pyridylsulfonamide

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.24 (3H, s), 3.62-3.67 (4H, m), 3.78-3.82 (4H, m), 6.55 (1H, d, J= 9.1 Hz), 7.14 (1H, d, J= 4.2 Hz), 7.21 (1H, dd, J= 4.9 - 3.6 Hz), 7.36-7.4 (1H, m), 7.53-7.6 (2H, m), 7.72 (1H, dd, J= 4.9 - 1.2 Hz), 7.93-8.01 (2H, m).8.1-8.12 (1H, m).8.39 (1H, d, J= 2.4 Hz).8.69 (1H, s).8.81 (1H, d, J= 4.6 Hz)

MS (ES) m/z = 561 (MH+)

HPLC = 98.7%

Example 91: N-methyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-2,4-dimethyl-5-thiazolylsulfonamide

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.22 (3H, s), 2.69 (3H, s), 3.35 (3H, s), 7.11 (1H, d, J= 4.6 Hz), 7.2 (1H, dd), 7.43-7.47 (1H, m), 7.59 (1H, m), 7.71 (1H, dd), 7.93-7.94 (1H, m), 7.97-8.02 (1H, m).8.09 (1H, dd, J= 3.7 - 1.1 Hz).8.68 (1H, s).8.81 (1H, d, J= 4.6 Hz)

MS (ES) m/z = 510 (MH+)

HPLC = 99.18%

Example 92: N-methyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-cyclopropyl-sulfonamide

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.95-1.06 (2H, m), 1.09-1.18 (2H, m), 2.4-2.51 (1H, m), 3.44 (3H, s), 7.16 (1H, d, J= 4.6 Hz), 7.19-7.23 (1H, m), 7.58-7.73 (3H, m), 7.96 (1H, m), 8.11 (1H, m), 8.16 (1H, m).8.71 (1H, s).8.82 (1H, d, J= 4.2 Hz)

MS (ES) m/z = 439 (MH+)

HPLC = 96.7%

Example 93: N-methyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-benzylsulfonamide

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.21 (3H, s), 4.39 (2H, s), 7.1 (1H, d, J= 4.6 Hz), 7.2-7.24 (1H, m), 7.33-7.47 (6H, m), 7.54-7.6 (1H, m), 7.71 (1H, d, J= 4.9 Hz), 7.87-7.92 (2H, m), 8.12 (1H, d, J= 3.3 Hz), 8.74 (1H, s).8.83 (1H, d, J= 4.6 Hz)
MS (ES) m/z = 489 (MH+)
HPLC = 97.95%

Example 94: N-methyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}—vinylsulfonamide

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.32 (3H, s), 6.08 (1H, d, J= 9.7 Hz), 6.26 (1H, d, J= 16.4 Hz), 6.51 (1H, dd, J= 16.4 - 9.7 Hz), 7.15 (1H, d, J= 4.2 Hz), 7.2 (1H, dd, J= 4.8 - 3.9 Hz), 7.53-7.64 (2H, m), 7.7 (1H, dd, J= 4.8 – 1.2 Hz), 7.94-7.98 (1H, m), 8.06-8.11 (2H, m)
MS (ES) m/z = 425 (MH+)
HPLC = 97.53%

Example 95: N-methyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-3,5-dimethyl-4-isoxazolylsulfonamide

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.12 (3H, s), 2.33 (3H, s), 3.31 (3H, s), 7.1 (1H, d, J= 4.5 Hz), 7.19-7.23 (1H, m), 7.52-7.66 (2H, m), 7.71 (1H, d, J= 5.5 Hz), 7.93-7.96 (2H, m), 8.07 (1H, d, J= 3.6 Hz), 8.69 (1H, s).8.82 (1H, d, J= 4.2 Hz)
MS (ES) m/z = 494 (MH+)
HPLC = 99.17%

Example 96: N-methyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-1,3,5-trimethyl-4-pyrazolylsulfonamide

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.09 (3H, s), 2.1 (3H, s), 3.24 (3H, s), 3.7 (3H, s), 7.1 (1H, d, J= 4.2 Hz), 7.2 (1H, dd, J= 4.8 - 3.6 Hz), 7.45-7.59 (2H, m), 7.71 (1H, dd), 7.9-7.98 (2H, m), 8.09-8.11 (1H, m), 8.67 (1H, s), 8.8 (1H, d, J= 4.2 Hz)
MS (ES) m/z = 507 (MH+)
HPLC = 94.68%

Example 97: N-methyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-propanesulfonamide

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.06 (3H, t, J= 7.5 Hz), 1.92-1.97 (2H, m), 3.02-3.08 (2H, m), 3.43 (3H, s), 7.16 (1H, d, J= 4.2 Hz), 7.19-7.23 (1H, m), 7.62-7.64 (2H, m), 7.72 (1H, m), 7.93-7.97 (1H, m), 8.11-8.14 (2H, m).8.71 (1H, s).8.83 (1H, d, J= 4.6 Hz)
MS (ES) m/z = 441 (MH+)
HPLC = 97.75%

Example 98: N-methyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-butanesulfonamide

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.93 (3H, t, J= 7.5 Hz), 1.44 (2H, m), 1.77-1.89 (2H, m), 3.04-3.11 (2H, m), 3.43 (3H, s), 7.16 (1H, d, J= 4.6 Hz), 7.2 (1H, dd, J= 5.2 - 3.9 Hz), 7.61-7.64 (2H, m), 7.71 (1H, dd, J= 5.2 - 1.2 Hz), 7.91-7.96 (1H, m).8.1 (1H, dd, J= 3.9 - 1.2 Hz).8.14 (1H, m).8.7 (1H, s).8.82 (1H, d, J= 4.3 Hz)

MS (ES) m/z = 455 (MH+)
HPLC = 98.54%

Example 99: N-methyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-cyclopentylmethane-sulfonamide

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.23-1.34 (2H, m), 1.56-1.66 (4H, m), 1.95-2.03 (2H, m), 2.32-2.44 (1H, m), 3.08 (2H, d, J= 7 Hz), 3.42 (3H, s), 7.16 (1H, d, J= 4.2 Hz), 7.2 (1H, dd, J= 4.9 - 3.9 Hz), 7.61-7.63 (2H, m), 7.71 (1H, dd, J= 4.9 - 1.2 Hz).7.91-7.96 (1H, m).8.09-8.14 (2H, m).8.7 (1H, s).8.82 (1H, d, J= 4.2 Hz)
MS (ES) m/z = 481 (MH+)
HPLC = 96.43%

Example 100: N-{3-[3-(5-methyl-[1,2,4]oxadiazol-3-yl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-methane-sulfonamide

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.71 (3H, s), 3.12 (3H, s), 7.08 (1H, d, J= 4.4 Hz), 7.1 (1H, a), 7.43-7.46 (1H, m), 7.57 (1H, t, J= 7.6 Hz), 7.80-7.83 (1H, m), 7.95 (1H, t, J= 2 Hz), 8.69 (1H, s), 8.8 (1H, d, J= 4.4 Hz)
MS (ES) m/z = 371 (MH+)
HPLC = 94%

Example 101: N-ethyl-N-{3-[3-(5-methyl-[1,2,4]oxadiazol-3-yl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-methane-sulfonamide

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.21 (3H, t, J= 7.2 Hz), 2.69 (3H, s), 2.95 (3H, s), 3.81 (2H, q, J= 7.2 Hz), 7.1 (1H, d, J= 4.8 Hz), 7.56-7.58 (1H, m), 7.64 (1H, t, J= 8 Hz), 8.04

(1H, d, J= 8 Hz), 8.09 (1H, t, J= 2 Hz), 8.69 (1H, s),8.817 (1H, d, J= 4.8 Hz)

MS (ES) m/z = 399 (MH+)

HPLC = 94%

Example 102: 5 mg tablets

Compound of Example 2	5.0	mg
Colloidal silicon dioxide	0.6	mg
Croscarmellose sodium	12.0	mg
Talc	4.0	mg
Magnesium stearate	1.5	mg
Polysorbate 80	1.0	mg
Lactose	75.0	mg
Hydroxypropyl methylcellulose	3.0	mg
Polyethylene glycol 4000	0.5	mg
Titanium dioxide E171	1.5	mg
Microcrystalline cellulose q.s. to	125.0	mg

Example 103: 10 mg capsules

Compound of Example 2	10.0	mg
Colloidal silicon dioxide	0.6	mg
Crospovidone	12.0	mg
Talc	4.0	mg
Magnesium stearate	1.5	mg
Lauryl sulfate sodium	1.5	mg
Lactose	77.0	mg
Gelatin	28.5	mg
Titanium dioxide E171	1.5	mg
Indigotin E132	0.02	mg
Microcrystalline cellulose q.s. to	155.0	mg

Example 104: oral drops

Compound of Example 2	0.5	g
Propylene glycol	10.0	g
Glycerin	5.0	g
Saccharin sodium	0.1	g
Polysorbate 80	1.0	g
Lemon flavor	0.2	g
Ethanol	25.0	mL
Purified water q.s. to	100.0	mL

Example 105: 2.5 mg tablets

Compound of Example 16	2.5	mg
Colloidal silicon dioxide	0.6	mg
Croscaramellose sodium	12.0	mg
Talc	4.0	mg
Magnesium stearate	1.5	mg
Polysorbate 80	1.0	mg
Lactose	75.0	mg
Hydroxypropyl methylcellulose	3.0	mg
Polyethylene glycol 4000	0.5	mg
Titanium dioxide E171	1.5	mg
Microcrystalline cellulose q.s. tp	125.0	mg

Example 106: 5 mg capsules

Compound of Example 16	5.0	mg
Colloidal silicon dioxide	0.6	mg
Crospovidone	12.0	mg
Talc	4.0	mg
Magnesium stearate	1.5	mg
Lauryl sulfate sodium	1.5	mg
Lactose	77.0	mg

Gelatin	28.5	mg
Titanium dioxide E171	1.5	mg
Indigotin E132	0.02	mg
Microcrystalline q.s.to	155.0	mg

Example 107: Oral drops

Compound of Example 16	0.25	g
Propylene glycol	10.0	g
Glycerin	5.0	g
Saccharin sodium	0.1	g
Polysorbate 80	1.0	g
Lemon flavor	0.2	g
Ethanol	25.0	mL
Purified q.s. to	100.0	mL